HISTOPATHOLOGICAL SPECTRUM AND NEURO-RADIOLOGICAL CORRELATIONS OF CHILDHOOD INTRACRANIAL BRAIN TUMORS IN KENYATTA NATIONAL HOSPITAL AND MOI TEACHING AND REFERRAL HOSPITAL

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DECLARATION

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Contents

DEDICATION

To Lynette, my loving wife, my daughters, Chelsea, Lisette and my adopted son Jamall, you are God's blessings to me.

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The Lord, God has been faithful to me throughout this project and I am very grateful to him.

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My colleagues in MMED pathology programme, I am grateful for your peer review and encouragement.

ABBREVATIONS

ATRT	Atypical Teratoid Rhabdoid Tumor
CBT	Childhood Brain Tumors
CBTRUS	Central Brain Tumor Registry of the United States
CIBT	Childhood Intracranial Brain Tumor
CNS	Central Nervous System
H/E	Hematoxylin and Eosin
IHC	Immunohistochemistry
KNH	Kenyatta National Hospital
MTRH	Moi Teaching and Referral Hospital
MRI	Magnetic Resonance Imaging
WHO	World Health Organization

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ABSTRACT

Background: Central nervous tumors are the leading solid tumors in the childhood population accounting for the majority of tumor mortality worldwide. The central nervous system is a specialized system which has on average 130 primary brain tumors. There are more than 100 different histological subtypes of brain tumors with varying incidences over regions. Previously childhood brain tumors (CBT) were uncommon in the African population, however there's increasing number of cases reported. There's limited data on childhood brain tumors as well as the histopathological distribution more so of primary brain tumors whose trends are being noted as increasing over time in Kenya. Our study aimed at assessing the spectrum as well as the level of correlation with imaging in diagnosis of brain tumors within the two settings.

Objectives: The main objective was to evaluate the histopathological spectrum and neuro-radiological correlations of childhood intracranial brain tumors in KNH and MTRH.

Methodology: Study site, design and population: This was a cross-sectional retrospective descriptive study done at KNH and MTRH. The study population was drawn from children who underwent treatment for brain tumors between 2015 and 2017 and whose tissue biopsies (87 cases) were available at the laboratory archives.

Data collection and analysis: Patient's biodata and histology reports including the intraoperative findings from the filed reports in the histopathology department were retrieved. The case blocks were retrieved for histological processing and analysis. Immunohistochemistry (IHC) was done on recommended cases and analyzed. Histopathological evaluation results were entered into Microsoft Excel 2013 and merged with the patients' biodata and previous histopathology reports using unique patient identification cards.

Univariate analysis was carried out to describe and summarize the data on the variables including age and gender. Appropriate descriptive statistics were reported depending on the type of data: Frequencies and proportions for categorical data such as tumor type, site, grade, imaging findings and/or measures of central tendency (mean/median/mode) and dispersion (SD/IQR) for patient's age. Bivariate analysis using chi-square tests was done to evaluate the association between the patients' gender and age group with brain tumor features. Chi-square statistics and corresponding p-values was reported. Data analysis was conducted at 0.05 level of significance.

Main Outcomes: Majority of the affected population were of ages 5-9 years with females at (54%) of the total population. The most affected site was infratentorial compartment (48.3%) with gliomas and medulloblastoma being equally distributed within it (23%). Gliomas and medulloblastoma were the most predominant tumors at 71.3% with gliomas leading at 48.3%. Majority of the gliomas were low grade (69%) with pilocytic astrocytoma being the most common subtype (42.9%). Immunohistochemistry tests were done in all the cases (9%) whose initial and final diagnosis were not tallying. The IHC panel tests conducted had results which all tallied with the final diagnosis after second review. The overall sensitivity for the diagnosis of brain tumors through radiology was at 69.4%. The level of correlation of histopathological to radiological diagnosis was statistically insignificant with P and kappa values of 0.814 and -0.024 respectively.

Conclusion: Gliomas and medulloblastomas were the commonest tumors at both centers similar to findings at centers in other studies around the world. Histopathological diagnoses have a high concordance of agreement among various morphologists. The level of correlation between histopathological and radiological diagnosis was high comparable to other findings conducted elsewhere within the country.

Recommendations: A standard neuro-radio-pathological proforma is recommended which synchronizes significant clinical, radiological and pathological details within the two departments with a view of ensuring data availability and synchronicity. There's need to expand the study to other centers in the country to gain the spectrum seen in the country. Some of the cases i.e. 8 cases had their final diagnosis altered after IHC was conducted hence need for follow up of the patients with regards to therapy altercation and prognostication.

1.0 INTRODUCTION

1.1 Background of the study

Central nervous tumors are the most common solid tumors in the childhood population, 3rd most common tumor overally and a leading mortality cause worldwide ranking second in U.S and Canada. (1) The CNS is a specialized system with on average 130 primary brain tumors. Generally, the brain's role and consequences of neuronal loss tends to explain the severity in primary brain tumors. (2) The overall average incidence rate in the US is 22.36 per 100,000 population. The incidence rate is 5.70 per 100,000 population for children and adolescents age <20 years, 5.47 per 100,000 population for children age <15 years.

Previously CIBT were uncommon in the African population, however there's increasing cases overtime for example in Olabiyi G et al 2016, it was noted as the fourth most common (3) while in Ojesina A et al 2002 there was a significant 2.2-12.9% increase over 5 decades.(4)

There's limited data on childhood brain tumors in Kenya. Mostert et al 2010 showed that brain tumors comprised 1% of all the childhood tumors reported. (5) There's limited data on histopathological distribution of CIBT among the young population, the associative risk factors especially within our setting and survival rates among this population in Kenya which is critical in evaluation of the successes of the various treatment modalities. This is also critical since the trend over time for CIBT is increasing. Moreover, there is need to have a system of analysis similar to CBTRUS over time to give a real picture on brain tumor trend countrywide.

2.0 LITERATURE REVIEW

2.1 Introduction

Brain tumors are classified either as benign or malignant. They can be broadly grouped as either primary or secondary with the secondary forms being malignant.

a. Primary Brain Tumors

They are composed of:

Benign tumors- They are the majority and have uniformly looking cells, have a slow growth, and do not metastasize. They can be life threatening when they are in vital areas as they exert pressure on sensitive nerve tissue or cause hydrocephalus. Malignant primary brain tumor arises in the brain as well.

Secondary (Metastatic) Malignant Brain Tumors

This occurs when malignant tumors spread to the brain from another part of the body system. They are thrice as common in adults. These tumors arise from the lung, breast, kidney, or skin melanomas.

b. Glial tumors (Gliomas)

These tumors on average constitute about 80% of the tumors and originate in glial cells. They are classified into four grades, Grades I and II (low-grade, slow growing) and grades III and IV (high-grade, fast growing).

Astrocytomas are glial tumors which arise from astrocytes and account for about 60% of all the primary brain tumors. They include:

- *Pilocytic astrocytoma* most common glioma types in children
- *Diffuse astrocytoma* occurs in both genders between ages 20 - 60
- *Anaplastic astrocytoma* occurs in adults of ages 30 – 60 years and in men.
- *Glioblastoma multiforme*, they're highly malignant and aggressive tumors, most common between ages 50 – 70 and constitute 10% of childhood brain tumors.
- *Oligodendrogliomas* They can be categorized as low-grade (grade II) or anaplastic (gradeIII).
- *Ependymomas* They are more common tumor types in children while in adults they occur in the ages between 40-50 years. They are grouped as myxopapillary, subependymomas, ependymomas, and anaplastic ependymomas.

c. Primary Non-Glioma Brain Tumors

1. *Medulloblastomas.* They are always located in the infratentorial compartment, are fast-growing aggressive tumors, constitute 15 - 20% of pediatric brain tumors.
2. *Pituitary Adenomas.* They constitute 10% of primary brain tumors, are benign and are more common in women.
3. *Lymphomas.* They can affect immunocompetent and immunocompromised individuals.

Benign non-glial brain tumors include:

1. *Meningiomas.* They account for about 25% of all primary brain tumors, are more common in women above 60 years of age. They are classified as benign meningioma, atypical meningioma and anaplastic meningioma.

FIGURE 1 :WHO CLASSIFICATION OF CNS TUMORS 2007

TUMOURS OF NEUROEPITHELIAL TISSUE

Astrocytic tumours	
Pilocytic astrocytoma	9421/1[1]
Pilomyxoid astrocytoma	*9425/3**
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Diffuse astrocytoma	9400/3
Fibrillary astrocytoma	9420/3
Gemistocytic astrocytoma	9411/3
Protoplasmic astrocytoma	9410/3
Anaplastic astrocytoma	9401/3
Glioblastoma	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Gliomatosis cerebri	9381/3
Oligodendroglial tumours	
Oligodendroglioma	9450/3
Anaplastic oligodendroglioma	9451/3
Oligoastrocytic tumours	
Oligoastrocytoma	9382/3
Anaplastic oligoastrocytoma	9382/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Cellular	9391/3
Papillary	9393/3
Clear cell	9391/3
Tanycytic	9391/3
Anaplastic ependymoma	9392/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	*9390/1**
Choroid plexus carcinoma	9390/3
Other neuroepithelial tumours	
Astroblastoma	9430/3
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	*9431/1**
Neuronal and mixed neuronal-glial tumours	
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	9493/0
Desmoplastic infantile astrocytoma/ ganglioglioma	9412/1
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Central neurocytoma	9506/1
Extraventricular neurocytoma	*9506/1**
Cerebellar liponeurocytoma	*9506/1**
Papillary glioneuronal tumour	*9509/1**
Rosette-forming glioneuronal tumour of the fourth ventricle	*9509/1**
Paraganglioma	8680/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	*9395/3**
Embryonal tumours	
Medulloblastoma	9470/3
Desmoplastic/nodular medulloblastoma	9471/3
Medulloblastoma with extensive nodularity	*9471/3**
Anaplastic medulloblastoma	*9474/3**
Large cell medulloblastoma	9474/3
CNS primitive neuroectodermal tumour	9473/3
CNS Neuroblastoma	9500/3
CNS Ganglioneuroblastoma	9490/3
Medulloepithelioma	9501/3
Ependymoblastoma	9392/3
Atypical teratoid / rhabdoid tumour	9508/3

TUMOURS OF CRANIAL AND PARASPINAL NERVES

Schwannoma (neurilemoma, neurinoma)	9560/0
Cellular	9560/0
Plexiform	9560/0
Melanotic	9560/0
Neurofibroma	9540/0
Plexiform	9550/0

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) (614A) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours and /1 for borderline or uncertain behaviour.

* The italicised numbers are provisional codes proposed for the 4th edition of ICD-O. While they are expected to be incorporated into the next ICD-O edition, they currently remain subject to change.

FIGURE 2 :WHO CLASSIFICATION OF TUMORS OF THE CNS 2016

WHO classification of tumours of the central nervous system

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M–mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	*9451/3*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*
Other astrocytic tumours	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, *RELA* fusion–positive	9396/3*
Anaplastic ependymoma	9392/3
Other gliomas	
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	9431/1
Astroblastoma	9430/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumour	9509/1
Rosette-forming glioneuronal tumour	9509/1
Diffuse leptomeningeal glioneuronal tumour	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	9395/3
Embryonal tumours	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3*
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumour with multilayered rosettes, NOS	*9478/3*
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	*9508/3*
Tumours of the cranial and paraspinal nerves	
Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0

Cont:

Melanotic schwannoma	9560/1
Neurofibroma	9540/0
Atypical neurofibroma	9540/0
Plexiform neurofibroma	9550/0
Perineurioma	9571/0
Hybrid nerve sheath tumours	
Malignant peripheral nerve sheath tumour	9540/3
Epithelioid MPNST	9540/3
MPNST with perineurial differentiation	9540/3
Meningiomas	
Meningioma	9530/0
Meningothelial meningioma	9531/0
Fibrous meningioma	9532/0
Transitional meningioma	9537/0
Psammomatous meningioma	9533/0
Angiomatous meningioma	9534/0
Microcystic meningioma	9530/0
Secretory meningioma	9530/0
Lymphoplasmacyte-rich meningioma	9530/0
Metaplastic meningioma	9530/0
Chordoid meningioma	9538/1
Clear cell meningioma	9538/1
Atypical meningioma	9539/1
Papillary meningioma	9538/3
Rhabdoid meningioma	9538/3
Anaplastic (malignant) meningioma	9530/3
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma**	
Grade 1	8815/0
Grade 2	8815/1
Grade 3	8815/3
Haemangioblastoma	9161/1
Haemangioma	9120/0
Epithelioid haemangioendothelioma	9133/3
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Ewing sarcoma / PNET	9364/3
Lipoma	8850/0
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma	8850/3
Desmoid-type fibromatosis	8821/1
Myofibroblastoma	8825/0
Inflammatory myofibroblastic tumour	8825/1
Benign fibrous histiocytoma	8830/0
Fibrosarcoma	8810/3
Undifferentiated pleomorphic sarcoma / malignant fibrous histiocytoma	8802/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8900/3
Chondroma	9220/0
Chondrosarcoma	9220/3
Osteoma	9180/0
Osteochondroma	9210/0
Osteosarcoma	9180/3
Melanocytic tumours	
Meningeal melanocytosis	8728/0
Meningeal melanocytoma	8728/1
Meningeal melanoma	8720/3
Meningeal melanomatosis	8728/3
Lymphomas	
Diffuse large B-cell lymphoma of the CNS	9680/3
Immunodeficiency-associated CNS lymphomas	
AIDS-related diffuse large B-cell lymphoma	
EBV-positive diffuse large B-cell lymphoma, NOS	
Lymphomatoid granulomatosis	9766/1
Intravascular large B-cell lymphoma	9712/3
Low-grade B-cell lymphomas of the CNS	
T-cell and NK/T-cell lymphomas of the CNS	
Anaplastic large cell lymphoma, ALK-positive	9714/3
Anaplastic large cell lymphoma, ALK-negative	9702/3
MALT lymphoma of the dura	9699/3
Histiocytic tumours	
Langerhans cell histiocytosis	9751/3
Erdheim–Chester disease	9750/1
Rosai–Dorfman disease	
Juvenile xanthogranuloma	
Histiocytic sarcoma	9755/3
Germ cell tumours	
Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumour	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/1
Mature teratoma	9080/0
Immature teratoma	9080/3
Teratoma with malignant transformation	9084/3
Mixed germ cell tumour	9085/3
Tumours of the sellar region	
Craniopharyngioma	9350/1
Adamantinomatous craniopharyngioma	9351/1
Papillary craniopharyngioma	9352/1
Granular cell tumour of the sellar region	9582/0
Pituicytoma	9432/1
Spindle cell oncocytoma	8290/0
Metastatic tumours	

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) (742A). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.
*These new codes were approved by the IARC/WHO Committee for ICD-O.
Italics: Provisional tumour entities. **Grading according to the 2013 *WHO Classification of Tumours of Soft Tissue and Bone*.

FIGURE 3 : Grading of selected CNS tumors according to the 2016 CNS WHO

WHO grades of select CNS tumours

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3 K27M–mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III
Other astrocytic tumours	
Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III
Ependymal tumours	
Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, *RELA* fusion–positive	II or III
Anaplastic ependymoma	III
Other gliomas	
Angiocentric glioma	I
Chordoid glioma of third ventricle	II
Choroid plexus tumours	
Choroid plexus papilloma	I
Atypical choroid plexus papilloma	II
Choroid plexus carcinoma	III
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	I
Gangliocytoma	I
Ganglioglioma	I
Anaplastic ganglioglioma	III
Dysplastic gangliocytoma of cerebellum (Lhermitte–Duclos)	I
Desmoplastic infantile astrocytoma and ganglioglioma	I
Papillary glioneuronal tumour	I
Rosette-forming glioneuronal tumour	I
Central neurocytoma	II
Extraventricular neurocytoma	II
Cerebellar liponeurocytoma	II
Tumours of the pineal region	
Pineocytoma	I
Pineal parenchymal tumour of intermediate differentiation	II or III
Pineoblastoma	IV
Papillary tumour of the pineal region	II or III
Embryonal tumours	
Medulloblastoma (all subtypes)	IV
Embryonal tumour with multilayered rosettes, C19MC-altered	IV
Medulloepithelioma	IV
CNS embryonal tumour, NOS	IV
Atypical teratoid/rhabdoid tumour	IV
CNS embryonal tumour with rhabdoid features	IV
Tumours of the cranial and paraspinal nerves	
Schwannoma	I
Neurofibroma	I
Perineurioma	I
Malignant peripheral nerve sheath tumour (MPNST)	II, III or IV
Meningiomas	
Meningioma	I
Atypical meningioma	II
Anaplastic (malignant) meningioma	III
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma	I, II or III
Haemangioblastoma	I
Tumours of the sellar region	
Craniopharyngioma	I
Granular cell tumour	I
Pituicytoma	I
Spindle cell oncocytoma	I

Imaging studies

Radiological imaging is useful as a tool for early detection of CIBT, tumor staging, monitoring the results of tumor resection, assessing therapeutic results of adjuvant therapies as well as detection of post-operative complications. Computed tomography (CT scan**)** is useful as a screening tool**.** It provides the bony anatomy and calcified lesions more adequately than MRI scan. Magnetic resonance imaging (MRI scan**)** provides details on soft tissues and anatomical evaluation better than CT scan. MRI scan is more specific and sensitive for tumor diagnosis and is used in children with suspicious CT scan findings or those with focal symptoms and signs highly suggestive of intracranial pathology. The international standard procedures comprise MRI scan with plain and contrast, FLAIR-fluid attenuated inverse recovery and DWI-diffusion weighted imaging modalities(13). Imaging has been a useful tool in the prediction of various tumour types. Emerging techniques including diffusion weighted MRI, perfusion MRI, biochemical analysis, proton MR spectroscopy have aided in enhancing level of accuracy in diagnosis of brain tumours. In a study by Latshaw R.E et al showed that it is possible to predict brain tumor histology by observing the change of effective atomic number with contrast enhancement in high grade gliomas as per vascularity, necrosis, pleomorphism and cellularity (14).Abuodha M et al in a study in MTRH, Kenya showed possibilities of diagnosing meningiomas radiologically on MRI with proven histopathologies though MRI demonstrated limitations in delineating the various subtypes (15). Ishtiaq A. et al in a study in Karachi, India correlating MRI usage and histopathological findings noted a level of accuracy of 94 %(16). In Kenya, Kibaya GN did a correlation study between the two aspects on the general population by use of CT scan and noted a level of agreement of an average of 40%(17). Zuriel et al in his correlation studies on gliomas noted a level of agreement of 16% which was quite low (18). However in a different study in Knh, Uni M. by

usage of MRI noted a level of agreement of 87.4% in gliomas probably attributed to improved reporting (19).

It is evident from various studies that different brain masses may exhibit similar radiological findings, a property which may pose some difficulties in reporting. These difficulties have been demonstrated through correlative studies between various imaging and histological findings of various brain masses. Norman E. et al studying histologically proven supratentorial gliomas concluded that CT scan provides a high degree of accuracy in the diagnosis of supratentorial gliomas with approximately 90% accuracy precontrast and 99% post contrast (20). Russel E.J et al on the other hand using 131 cases of histologically confirmed meningiomas noted 7% of the cases that were misdiagnosed with atypical presentation being the main reason for the misdiagnosis. Savouiando M. et al reported a hyper dense area with a proven meningioma which was later proved to be a metastatic deposit from breast cancer (21).

Other Imaging tests include sonography which is utilized in infants with open fontanelles. Angiographic studies (CTA/MRA) are used to evaluate the involvement of major arteries and dural venous sinuses. Positron emission tomography (PET) and other functional modalities are utilized in the assessment of treatment outcome and the biological activity of the residual tumor, selection of biopsy site and delineation of the tumor margins from the normal brain.

Role of Immunohistochemistry (IHC)

Biological markers are used as adjuncts to morphology and depicting tumor behaviour. The technique link the antibody to an antigen and if specific then a visible stain will be noticed microscopically.

Immunohistochemistry is categorised into four main components: fixatives, retrieval of the antigen, sections types and methods of detection. Fixatives used should preserve and stabilize cells protecting them from rigors of processing and staining techniques. Antigen retrieval is used to expose antigens after fixations and the common methods involve microwave heating, pressure cooking and enzyme digestion. Detection methods commonly used are calorimetric, enzyme mediated and fluorescence methods. Sample types include frozen sections and paraffin sections.

Immunohistochemistry offers greater diagnostic specificity where morphology alone is inconclusive. There are various studies that have been conducted to depict the various IHC panels on various brain tumors.(31,32). Different tumors express specific antigens e.g glial tumors express GFAP which other tumors e.g meningiomas and Pnets do not. Pnets on the other hand express CD99 antigens which choroid plexus tumors, ependymomas and glial tumors do not. Our study utilized these IHC panels to improve diagnosis in the cases whose initial and final histomorphological diagnosis were not tallying. Newer markers have been introduced including IDH in for glial tumors which have roles in detecting tumor response to the various treatment modalities and for prognostication. However such markers which have been incorporated into the WHO 2016 brain tumor classification are rare and expensive hence are not often utilized. Tissue microarray technology is on the rise and it allows the fast screening of many tumor samples simultaneously which has been applied in IHC in expression of various markers e.g. p53. Immunohistochemistry as a technique has been used

to solidify diagnosis where pattern, cellular characteristics are missing or inconclusive.

Epidemiology of Brain Tumors

Brain tumors are the commonest solid tumors among those age <20 years and a leading mortality cause with an incidence rate of 5.47 per 100,000 population yearly.

The incidence rate of all brain tumors according to CBTRUS 2013 was 22.36 cases per 100,000 with the rate was higher in females at 24.46 per 100,000 than in males 20.10 per 100,000. The paedriatic incidence was 5.47 and 5.67 cases per 100,000 for ages <15 and <20 years respectively.

Incidence rates study have been conducted in various other countries beyond the US. In Germany, a study by Kaatsch P et al 1999 noted an incidence rate of 2.6 per 100,000 for children aged <15 years.(22) This is a much lower incidence than the one in the CBTRUS report probably attributed to the lower age group sampled.

In a study by Kenneth K. et al 2013 in Kuwait, the incidence rate was 11.2/ million children of ages <20 years with both tumor grades in the study being noted to peak in 0-4 and 5-9 years respectively. (23)

In the Mwang'ombe et al. study done locally in KNH in 2000 retrospectively noted an overall incidence of 3.7 and 2.6 per 100,000 for males and females respectively with rates being higher in developed countries. Closer a field in east Africa, incidence rates of less than 10 % have been noted in Uganda.

Brain tumor locations and gender vary among the various tumor types and subtypes for various regions. In the US, frontal, temporal, parietal and occipital lobes constituted 19.0% of all tumors with the commonest site being the meninges at 37%. For ages <20 years majority of the tumors were located in the pituitary and pineal glands (17.7%). For those aged <15 years the cerebellum comprised the majority of the tumors at 18.0%.

Gliomas accounted for approximately 53.1% of tumors in children age <15 years in the US. On embryonal tumors, medulloblastoma, atypical teratoid/rhabdoid tumor (ATRT), and

primitive neuroectodermal tumor (PNET) accounted for 63.7%, 15.4%, and 12.5%, respectively. In a study by Perkin D et al 1998 in the US, the main tumor groups in children were astrocytomas (38-50%) followed by medulloblastomas with ependymomas being the least. (25)

In another study in Germany by Kaatsch K. et al 1999 it was noted that the commonest tumors were astrocytomas (41.7%) followed by the medulloblastomas with craniopharyngiomas being the least. Majority of these tumors were located mainly in the cerebellum (27.9%) and cerebrum (21.2%). (14) In a different study by Kenneth K et al 2013 in Kuwait, the most common tumors were astrocytoma at 37% with ependymal tumors being the least at 8%. The most common tumor location was cerebellum at 47% in childhood. (23)

In Africa, Olabiyi G et al 2016 in Nigeria noted astrocytic tumors as the most common followed by embryonal tumors with the least being craniopharyngiomas. (3) Uche E et al 2013 in yet another study noted that low-grade astrocytoma and medulloblastoma had equal distribution at 25 % as the most common tumors. (26).

In Kenya, an initial study by Mwang'ombe et al 2000 noted that gliomas were the commonest tumors at 45.8% affecting mainly males. (24) In yet another review in 2005 they noted that medulloblastoma and low grade gliomas were the most common tumours in children compared to adults where high grade glioma and meningioma were the most common. (27)

Other studies done in Kenya including the ones above have mainly been conducted in the general population and not specifically children. However there's one study conducted by Wanyoike PK in 2004 where he focused on posterior cranial fossa tumors in children aged between 2 and 16 years. In his study majority of the gender were females with medulloblastomas being the most common tumors. Of note was that astrocytomas were equally represented in both gender. (33)

2.8 JUSTIFICATION

Brain tumors are the leading solid tumors quantitatively and are a leading cause of tumor related deaths in the developing and developed countries.(1) In Kenya, cancer is reported as third leading and second leading cause of death overally and among the non-communicable diseases respectively. (5) This data is general for the whole population and for all the cancers hence there's need to clearly define the occurrence and death rates among the various childhood malignancies including brain tumors.

There are countries across Europe and Africa which have carried out studies to ascertain the histopathological trend of childhood brain tumors with the US leading in having a 5 yearly updated review of CIBT. Across Africa, most of the studies have been conducted in Morocco and Nigeria mainly based on morphology and its increasing trend in children noted as compared to the overall population. (30) The histopathological spectrum of primary brain tumors in children however remains unknown in Kenya. There's need to set up one in Kenya with a possible 4-5yearly review. The study in addition to providing useful information on the two issues above for purposes of planning and management of CIBT by having a proper registry provides a platform to be able to study epidemiological trends and to aid histopathological departments to set up a continual evaluation on its performance in diagnosis as well as utility of IHC and assess its level of correlation with neuro-radiological diagnosis.

2.9 RESEARCH QUESTION

What are the current demographics, histological variants (WHO) and level of correlation in histopathologal and neuro-radiological diagnosis of CIBT?

2.10. OBJECTIVES

2.10.1. Broad Objectives

To describe the histopathological spectrum and neuro-radiological correlations of childhood Intracranial brain tumors in Kenyatta National Hospital (KNH) and Moi Teaching and Referral Hospital (MTRH).

2.10.2 Specific Objectives

1. To determine the demographic characteristics of brain tumors in children presenting at the KNH and MTRH between 1st January 2015 and 31st December 2017.
2. To determine the histopathological types and subtypes of childhood intracranial brain tumors using the WHO 2007 criteria in KNH and MTRH between 1st January 2015 and 31st December 2017.
3. To correlate the histopathological findings of CIBT with the radiological findings for the duration between 1st January 2015 to 31st December 2017 in KNH and MTRH.

3.0 METHODOLOGY

Study Site

The CIBT biopsies used in this study were obtained from the histopathological laboratory archives in KNH and MTRH. The two centers were selected with a view of retrieving adequate sample size for evaluation. The patients' biodata and initial diagnosis of CIBT were obtained from the patients' records at the radiological and human pathology departments.

Study Design

This was a cross-sectional retrospective descriptive study whose utility involved in-patient records and archived CIBT tissue biopsies collected between 1st January 2015 to 31st December 2017 from childhood intracranial brain tumor (CIBT) cases at KNH and MTRH.

3.1 Study Population

The study population were drawn from CIBT tissue biopsies of children aged not more than 15 years which had a confirmed diagnosis of CIBT lesion at KNH and MTRH (87 case blocks) between 1st January 2015 and 31st December 2017.

3.1.1 Case definition for CIBT

3.1.2 Inclusion criteria

- Childhood intracranial brain tumor tissue blocks of cases (≤15 years) and with a confirmed diagnosis of CIBT lesion.
- Availability of archived CIBT tissue biopsy blocks relating to the patients' biodata cases for the prescribed age set above at the histopathology laboratory.

3.1.3 Exclusion criteria

- Patients whose biodata were available but whose blocks could not be retrieved in the histopathology lab.

- Patients with missing clinical information e.g. age, variations in coding / numbering details in the clinical forms and tissue blocks e.g. S/10/18 on clinical form and S/22/18 on corresponding tissue block.

3.2 **Sample Size Calculation**

The purpose of this study was to classify brain tumors in the selected tissue cases based on their histopathological assessment. The outcome was to be expressed in terms of proportion of a given tumor type in the study sample. Sample size was calculated using Dancun formulae (1999) for estimation of single population proportion

$$n = \frac{N{Z_{\alpha/2}}^2 P(1-P)}{d^2(N-1) + {Z_{\alpha/2}}^2 P(1-P)}$$

Where:

n> minimum sample size

N=Total estimated accessible tissue biopsy cases=100

$Z_{\alpha/2}$=Standard normal critical value at α-level of significance for a two-sided test (α=0.05, $Z_{\alpha/2}$=1.96)

P= estimated prevalence of a given type of childhood brain tumor among cases of CBT (p=0.14%) based on the proportion of (germ cell tumors) among CBT cases in a study conducted in Nigeria (Olabiyi G et al, 2016)

d=Margin of error (d=0.05)

Using the defined parameters, the minimum required sample size was, n= 70 cases

3.3 **Sampling method**

Given the few number of CIBT cases seen in the facilities, all cases with archived CIBT biopsies meeting the inclusion criteria were included in the study.

3.4 Data collection

Following ethical approval by KNH-UON and MTRH-MOI UNIV. ERC, patient record files from the selected cases were retrieved from the hospital information system department (neuro- surgical section) and histopathological departments upon making necessary requests and documentations.

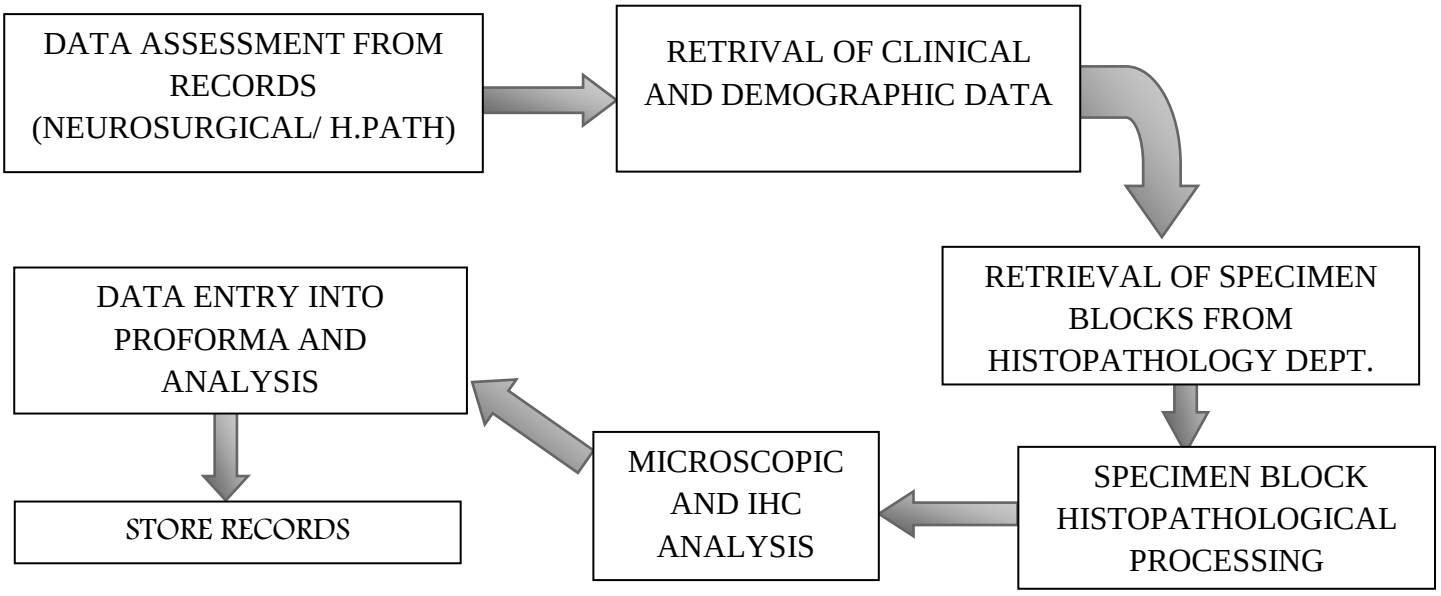
From the hospital information system department access to the in-patient records involved assessment of the patients' files to which the tissue cases had been transcribed which provided information on the variables. The patients' age, gender and intra-op findings were documented into the structured data collection tool. Evaluation of their radiological findings indicated on the patients' files were noted. This was followed by correlation with the information and films stored in the neuro-radiological department. This was essential to validate the radiological information.

Data was collected on the following variables;

- Demographic characteristics- age and gender
- Tumor site
- Tumor types and subtypes
- Tumor grade
- Radiological diagnosis

- Initial and current histopathological diagnosis critical for correlation and where there was no tally in diagnosis, IHC was conducted to ascertain the final histopathological diagnosis.

The blocks to be analyzed were then retrieved from the storage section using specially assigned coded numbers e.g. S/10/18 which are usually indicated on the request form accompanying the organ being brought to the department for processing. These coded numbers are indicated on the request form, remnants of the organ (noted on the storage container), the tissue blocks processed as well as on the final report. This is significant for traceability of the specimens. Once retrieved, the tissue blocks were processed, analyzed by the researcher and confirmed by the supervisors. Immunohistochemistry was done on recommended cases guided by the supervisors. (Refer to appendix I)



3.5 Data management and analysis

Once collected, data was entered and stored in Microsoft Excel 2013, coded and analyzed using STATA version 13.

Univariate analysis was done to summarize the data/variables. For continuous/discrete variables such as patient age, histograms were plotted to show the distribution; measures of central tendency (means/medians/mode) and dispersion (SD/ IQR) were reported depending on the distribution. For categorical data such as tumor type, bar/pie charts were plotted to show the distribution; frequencies and proportions were reported.

Chi-square test of association was used to evaluate the association between patient's demographic characteristics (age and gender) and histopathological findings (CBT type and subtypes). Chi-square statistics and corresponding p-values were reported. Cramer's V coefficient was computed to evaluate the agreement between initial and subsequent (final) histopathological diagnosis after review; Cramer's V statistic was reported. Sensitivity of radiological diagnosis was also reported. Analysis was conducted at 0.05 α-level of significance.

3.5 **Quality assurance**

3.5.1.1 **Pre-Analytical Stage**

Pathology reports and specimen blocks were checked to confirm whether they corresponded to each other. Data was carefully entered into the proforma to avoid mix-up and transcription errors. Blocks and slides were properly labeled.

3.5.1.2 **Analytical Stage**

Quality control was done on all the stains before use. The stains were kept covered. The reagents were stored in a refrigerator at the recommended temperature by the manufacturer. Once retrieved, the tissue blocks were prepared into slides after microtome sectioning and dewaxing in a water bath and stained using standard hematoxylin- eosin. Contamination of slides was avoided by using standard staining racks, while standard operating procedures were used in every stage. The slides were examined initially by the PI and the two consultant

pathologist. Incase of diagnostic discrepancies with the initial histopathological diagnosis, IHC was conducted on such blocks to ascertain which of the two i.e. initial and final diagnosis was correct by using antibodies specific to each of the two respective tissue antigens. Where there was specificity, staining would be noted in either of the two tissues in the nucleus or cytoplasmic membrane of the definate tumor and this tumor type would then be the final diagnosis. The choice of IHC panel depended upon the antigen characteristic of that particular tumor e.g. GFAP and CD99 expression by glial tumors and PNETs respectively.

3.5.1.3 **Post-Analytical Stage**

The final histopathological diagnosis after morphology where there was no discordance in findings and in cases where IHC were conducted on the selected cases were transcribed onto the reporting proforma for each of the cases analyzed. To ensure precise interpretation of results all slides were verified before release of the report. Care was taken to avoid post-transcription errors. In cases where there were discordance in diagnosis and IHC conducted, a final report was made and released to neurosurgical department for patient follow up detailing the diagnostic changes made and the IHC tests done on such tumors to confirm the new diagnosis.

3.6 **. Ethical consideration**

Formal approval to conduct this study was sought from KNH/UON-ERC, MTRH-MOI University ERC (Ethics and review commission) and study commenced after formal approval.

Confidentiality was maintained in all the information retrieved and were used for purposes of the research only.

3.7 **Data dissemination**

The results of the study were presented to the Kenyatta National Hospital - UON, MTRH-MOI University both in department of Human Pathology and Neurosurgery. It will also be published in journals and presented in upcoming seminars.

CHAPTER 4

RESULTS

4.1. Demographic characteristics

A total of 87 childhood brain tumor biopsies seen between the 1st January 2015 and 31st December 2017 were examined. Twenty patients were from MTRH and 67 patients were from KNH.

N= 87 cases

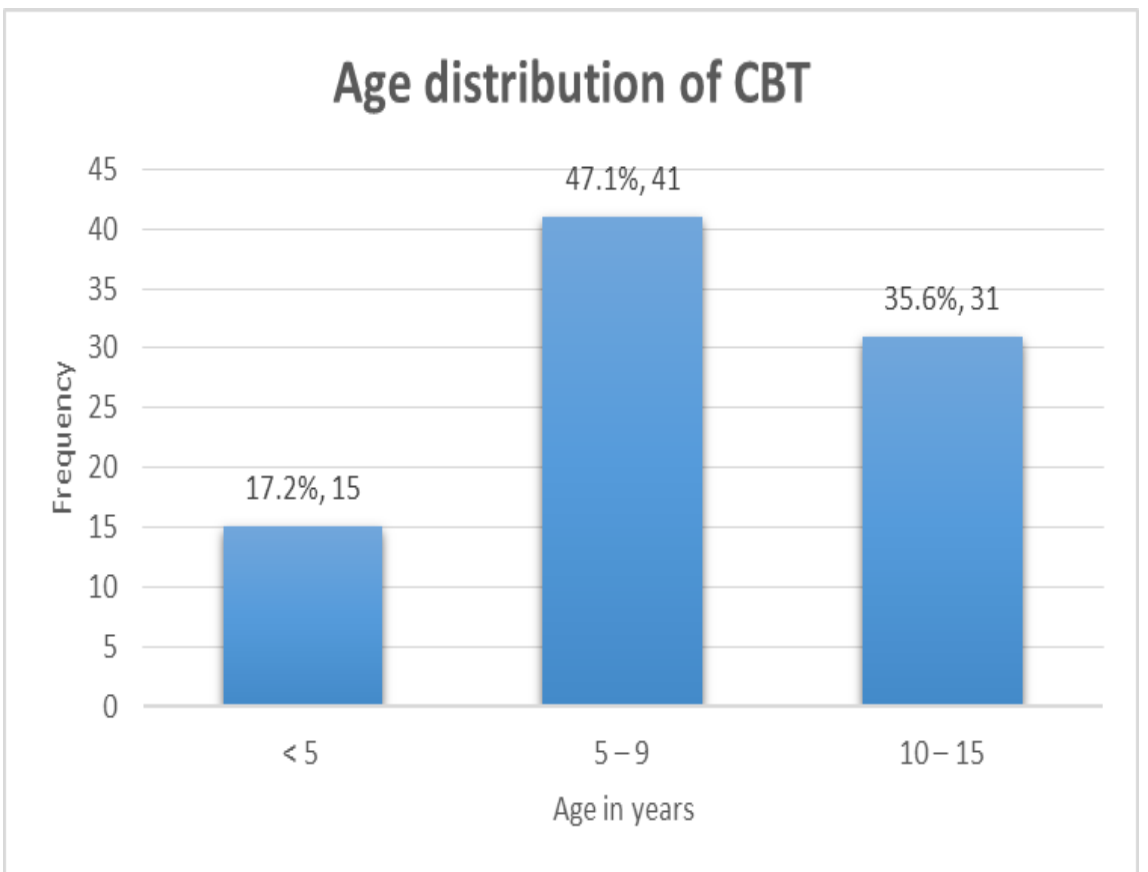


Figure 4: A histogram showing age distribution of the CBT patients in the study.

The demographic characteristics showed that majority of the patients i.e.41 (47.1%) were of age 5 to 9 years. The mean age was 7.9 (S.D 3.5) years. The median age was 7.0 years. (Figure 4).

N=87 cases

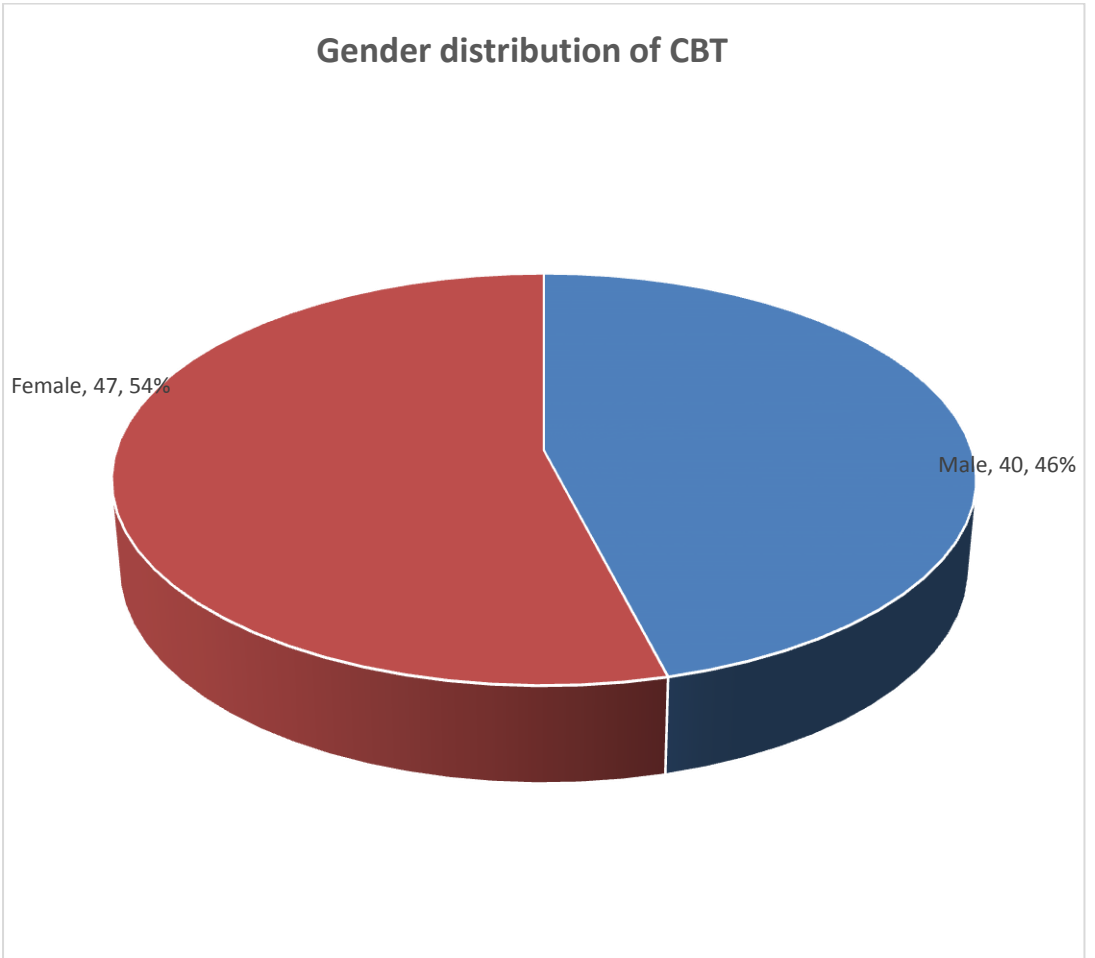


Figure 5: A Pie chart showing Distribution of CBT cases as per Gender

Majority of the CIBT were from the female gender accounting for 54%, while males were 46%. The male to female ratio was 0.85:1. Variation in gender was statistically insignificant at P=0.52 (Figure 5)

N=87 cases

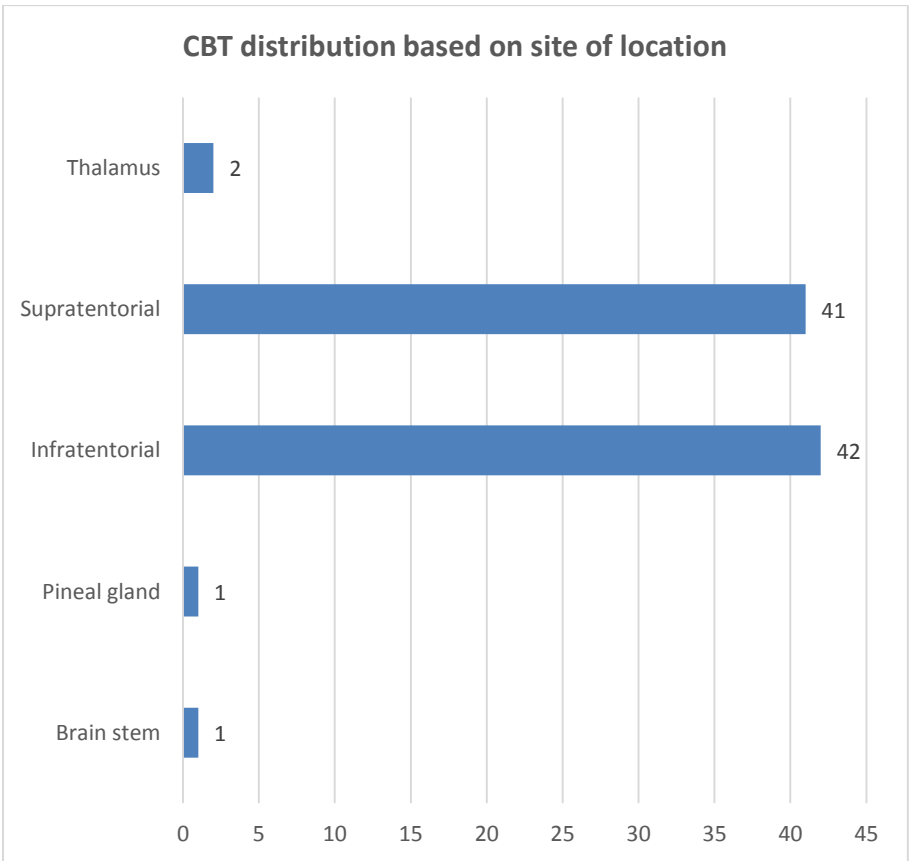


Figure 6: Histogram showing distribution of tumors based on site of location

Majority of the tumors were distributed in the infratentorial compartment 42 (48.3%) followed by supratentorial 41 (47.1%), thalamus at 2 (2.2%), pineal gland and brainstem were equally distributed at 1 (1.1%). (Figure 6)

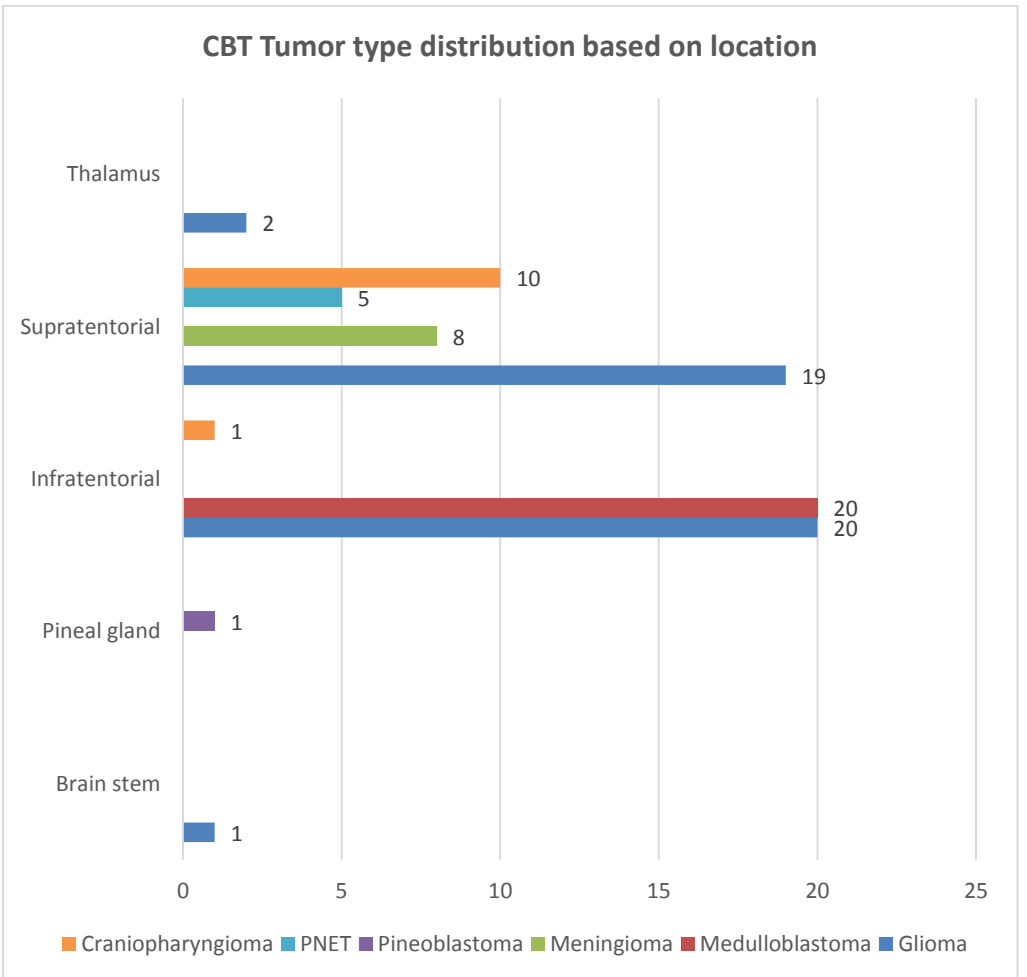


Figure 7: Histogram showing brain tumor type distribution based on location

Gliomas 20 (23%) and medulloblastoma 20 (23%) were the main tumors located in the infratentorial compartment. Gliomas 19 (21.8%) were as well the main tumors localized in the supratentorial area. The other tumors are distributed as per indicated above with some tumor types being localized in more than one site. (Figure 7)

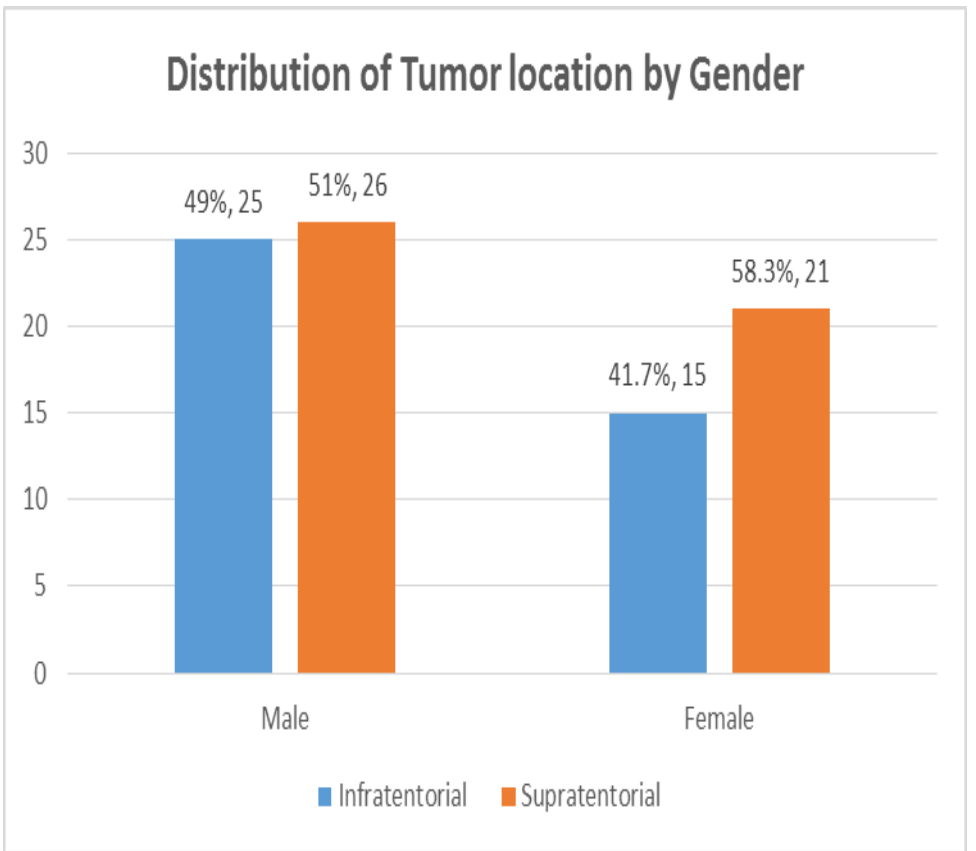


Figure 8: Histogram showing brain tumor distribution as per Site

Majority of the tumors were within the supratentorial area in both genders at 51% and 58.3% respectively for both males and females. On testing tumor location and gender, there was no statistical significance, P= 0.498 (Figure 8)

N=87 cases

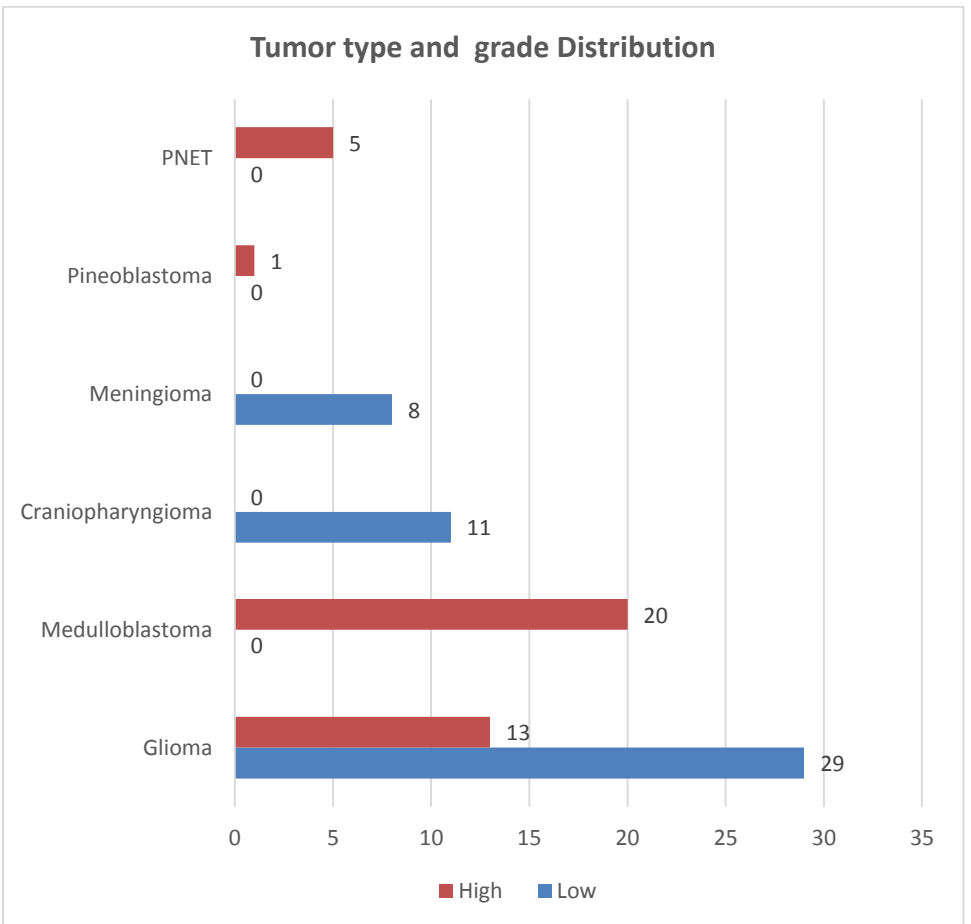


Figure 9: Histogram showing brain tumor types distribution as per grades

Majority of the gliomas were low grade, 29 (33.3%) as well as all the meningiomas and craniopharyngiomas. All the medulloblastomas, PNET and pineoblastoma were all high grade. In this case, low and high grades refer to low and high tumor replication index respectively. Variation in grade in gliomas was found to be statistically significant at P= 0.02 (Figure 9)

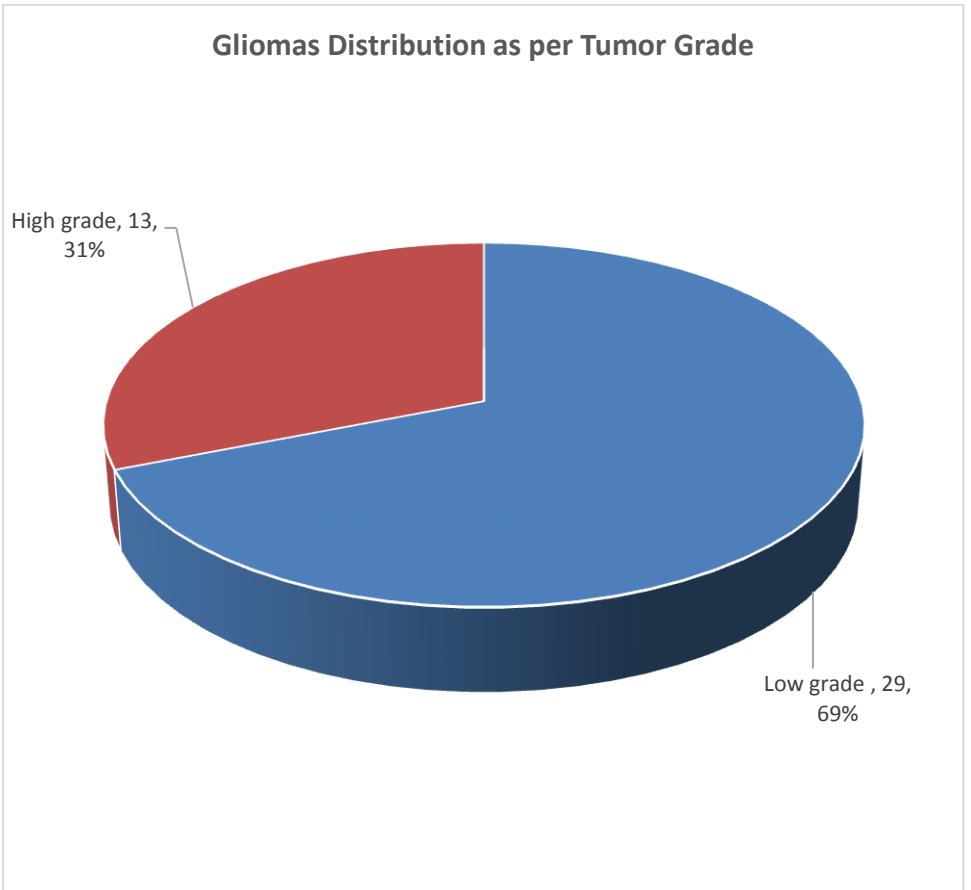


Figure 10: Pie chart showing glioma distribution as per tumor grade

Majority of the glial tumors were of Low grade at 69% as compared to the high grade variants at 31%. (Figure 10)

4.2. Histological Types and Subtypes

Table 1: Brain Tumor Distribution as per Histological Types and Subtypes

Tumor type	Tumor subtype	
Neuroepithelial tissue Tumors (‘’Gliomas”)	Diffuse Astrocytoma	2
	Anaplastic Astrocytoma	2
	GBM	7
	Oligoastrocytoma	1
	Pilocytic astrocytoma	18
	Pleomorphic Xanthoastrocytoma	1
	SEGA	2
	Ependymoma	2
	Anaplastic Ependymoma	4
	CP Papilloma	1
	Ganglioglioma	2
Sellar Region Tumors	Craniopharyngiomas	11
Medulloblastoma (Embryonal Tumors)	Classic Medulloblastoma	15
	Desmoplastic Medulloblastoma	4
	Medulloblastoma with extensive nodularity	1
Meningioma	Atypical Meningioma	3
	Meningoethelial Meningioma	1
	Syncytial Meningioma	3
	Transitional Meningioma	1
Pineal Region Tumors	Pineoblastoma	1
PNET (Embryonal Tumors)	PNET	5
TOTAL (N)		87

The table above showed results of the tumor type and their subtypes. The histological characteristics of the tumor variants are as shown.

N=87 cases

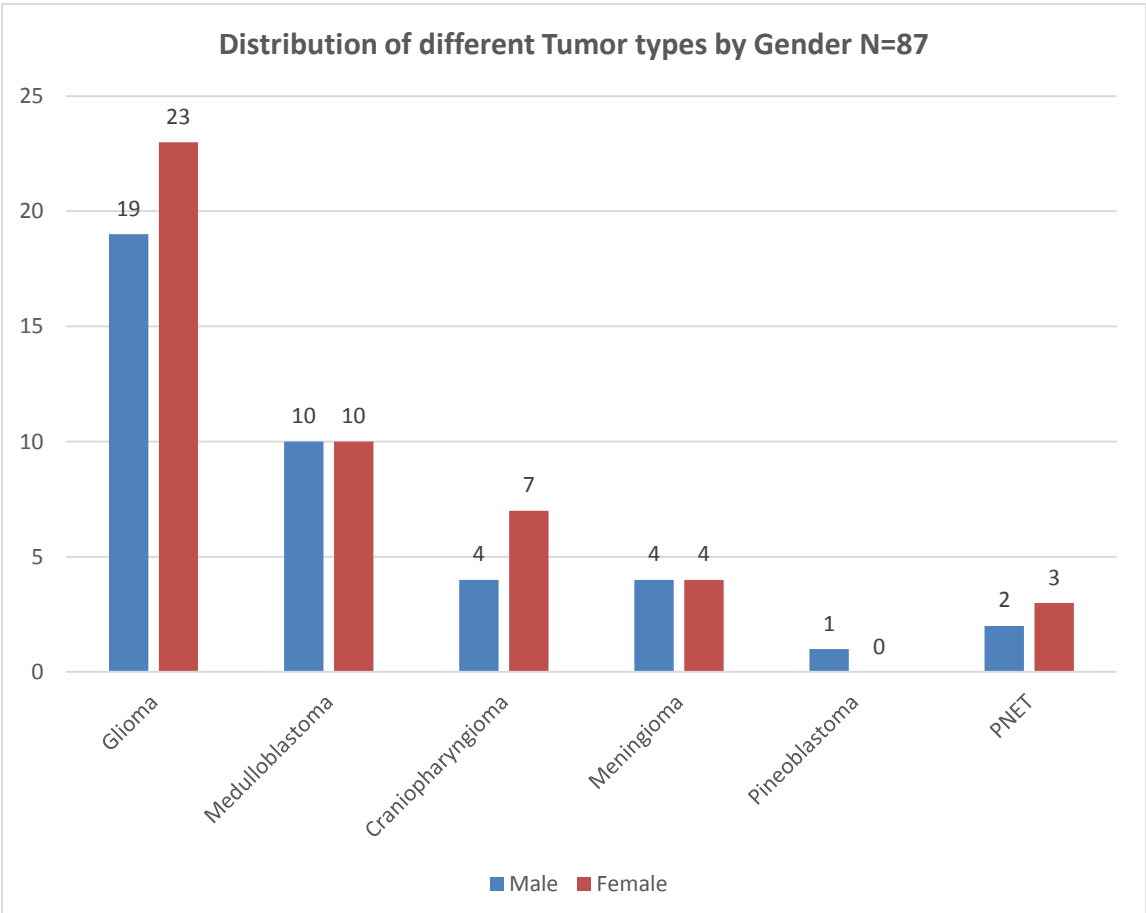


Figure 11: Histogram showing brain tumor type distribution as per gender

More females than males were affected by gliomas, craniopharyngiomas (suprasellar tumors) and Pnets. Medulloblastomas and meningiomas had equal distribution among the genders with a single case of pineoblastoma reported in the male gender. Variation in gliomas and craniopharyngiomas with gender were found to be both stastistically insignificant at P= 0.644 and 0.549 respectively. (Figure 11)

N=87 cases

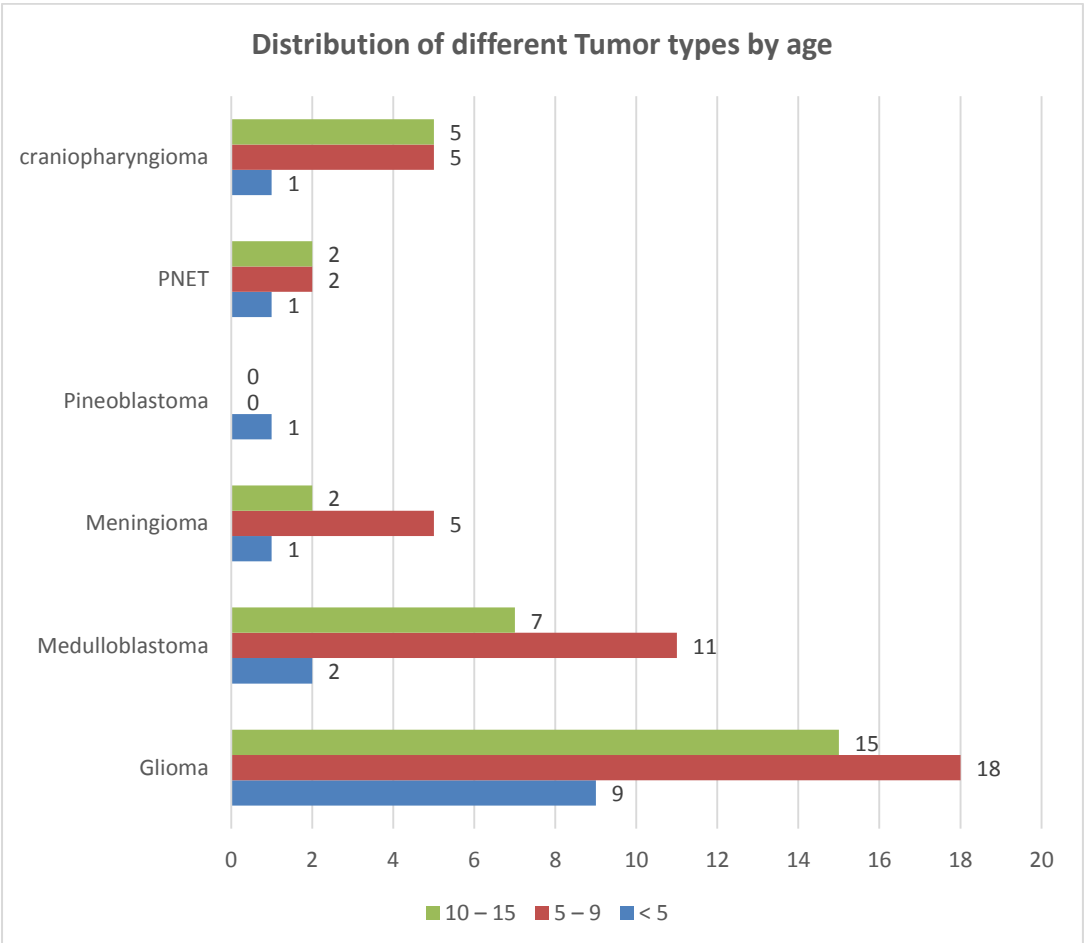


Figure 12: Histogram showing distribution of different tumor types by age groups

Majority of the children within the 5-9 year age range were affected by gliomas, medulloblastomas, meningiomas, PNET and craniopharyngiomas followed by the 10-15 year age range with under 5's being the least affected. Craniopharyngiomas and PNETs had equal distribution among the 5-9 and 10-15 year age range. (Figure 12)

Table 2: Distribution of the Various Tumor Subtypes as per Gender

Tumor type	**Tumor subtype**	Male	Female
Neuroepithelial tissue Tumors (‘’Gliomas”)	Diffuse Astrocytoma	1 (2.5)	1 (2.1)
	Anaplastic Astrocytoma	0 (0.0)	2 (4.3)
	GBM	4 (10.0)	3 (6.4)
	Oligoastrocytoma	1 (2.5)	0 (0.0)
	Pilocytic astrocytoma	9 (22.5)	9(19.1)
	Pleomorphic Xanthoastrocytoma	1 (2.5)	0 (0.0)
	SEGA	1 (2.5)	1 (2.1)
	Ependymoma	0 (0.0)	2 (4.3)
	Anaplastic Ependymoma	2(5.0)	2(4.3)
	CP Papilloma	0 (0.0)	1 (2.1)
	Ganglioglioma	0 (0.0)	2 (4.3)
Sellar Region Tumors	Craniopharyngiomas (Adamantinomatous)	4 (10.0)	7(14.9)
Medulloblastoma (Embryonal Tumors)	Classic Medulloblastoma	8 (20.0)	7(14.9)
	Desmoplastic Medulloblastoma	2 (5.0)	2 (4.3)
	Medulloblastoma with extensive nodularity	0 (0.0)	1 (2.1)
Meningioma	Atypical Meningioma	1 (2.5)	2 (4.3)
	Meningoethelial Meningioma	1 (2.5)	0 (0.0)
	Syncytial Meningioma	1 (2.5)	2 (4.3)
	Transitional Meningioma	1 (2.5)	0 (0.0)
Pineal Region Tumors	Pineoblastoma	1 (2.5)	0 (0.0)
PNET	PNET	2 (5.0)	3 (6.4)
TOTAL (N)		40	47

The table above showed the distribution of different tumor subtypes with respective gender.

Table 3: Childhood brain tumor subtype distribution as per age ranges

Tumor type	Tumor subtype	<5yrs	5-9yr	10-15
Neuroepithelial tissue Tumors (‘’Gliomas”)	Diffuse Astrocytoma	1 (6.7)	0 (0.0)	1 (3.2)
	Anaplastic Astrocytoma	0 (0.0)	1 (2.4)	1 (3.2)
	GBM	1 (6.7)	3 (7.3)	3 (9.7)
	Oligoastrocytoma	0 (0.0)	0 (0.0)	1 (3.2)
	Pilocytic astrocytoma	3 (20.0)	7 (17.1)	8 (25.8)
	Pleomorphic Xanthoastrocytoma	0 (0.0)	1 (2.4)	0 (0.0)
	SEGA	0 (0.0)	2 (4.9)	0 (0.0)
	Ependymoma	1 (6.7)	1 (2.4)	0 (0.0)
	Anaplastic Ependymoma	2 (13.3)	2 (4.9)	0 (0.0)
	CP Papilloma	0 (0.0)	0 (0.0)	1 (3.2)
	Ganglioglioma	1 (6.7)	1 (2.4)	0 (0.0)
Sellar Region Tumors	Craniopharyngiomas	1 (6.7)	5 (12.2)	5 (16.1)
Medulloblastoma (Embryonal Tumors)	Classic Medulloblastoma	2 (13.3)	9 (22.0)	4 (12.9)
	Desmoplastic Medulloblastoma	0 (0.0)	2 (4.9)	2 (6.5)
	Medulloblastoma with extensive nodularity	0 (0.0)	0 (0.0)	1 (3.2)
Meningioma	Atypical Meningioma	1 (6.7)	2 (4.9)	0 (0.0)
	Meningoethelial Meningioma	0 (0.0)	0 (0.0)	1 (3.2)
	Syncytial Meningioma	0 (0.0)	2 (4.9)	1 (3.2)
	Transitional Meningioma	0 (0.0)	1 (2.4)	0 (0.0)
Pineal Region Tumors	Pineoblastoma	1 (6.7)	0 (0.0)	0 (0.0)
PNET	PNET	1 (6.7)	2 (4.9)	2 (6.5)
TOTAL (N)		15	41	31

The previous table showed the distribution of the various tumor subtype variants with their varying age ranges. Majority of the glial tumors were pilocytic astrocytoma which were dominant within the 10-15yr and 5-9 yr. age range (1st two decades). Majority of the medulloblastoma being of the classic type and meningiomas were within the 5-9 yr. age range. Majority of the craniopharyngiomas were equally distributed within the 5-9 yr. and 10-15 yr. age range.

4.3. Histopathological Findings

Table 4: Histopathological Correlation between Previous and Current Diagnosis of the Tumor subtype Variants:

Number of cases for IHC = (8)	Previous histopath diagnosis	Finalhistopath diagnosis	Immunohistochemistry panels and results	Final diagnosis after Immunohistochemistry
1	Meningioma	Craniopharyngioma	Cytokeratin +ve EMA -ve Vimentin -ve	Craniopharyngioma
2	PNET; CP Carcinoma	PNET	CD 99 +ve Cytokeratin –ve EMA -ve	PNET
3	GBM	Anaplastic Astrocytoma	GFAP +ve KI 67 –ve (<5%)	Anaplastic Astrocytoma
4	Anaplastic Oligodendroglioma	Oligoastrocytoma	KI 67 –ve (<5%)	Oligoastrocytoma
5	PNET	Ependymoma	CD 99-ve GFAP +ve EMA +ve	Ependymoma
6	PNET	GBM	CD 99 –ve GFAP +ve	GBM
7	Round Blue Cell Tumor	PNET	CD 99+ve GFAP –ve	PNET
8	PNET	Ependymoma	CD 99 –ve EMA +ve GFAP +ve	Ependymoma

The previous table showed a list of tumors which had their initial diagnosis as indicated, a diagnosis from various pathologists who first made them morphologically. The final histopathological diagnosis is the diagnosis made after the various blocks had been processed and the slides analyzed by the two supervisors morphologically. In each of these scenarios, there were disagreement in morphological diagnosis hence in each, respective IHC panel was done to distinguish between the two tumors and the final diagnosis was made dependent on which antigenic features expressed by one tumor as opposed to the other as indicated in table 4.

The pictorials are for the various tumors (numbered 1-8) subjected to immunohistochemistry as indicated in table 4. Each number (1 to 8) has a morphological view of the final histopathological diagnosis of the tumor and in each the particular IHC panel that were conducted with controls and the respective result outcome as indicated in table 4.

Table 5: Overall Histopathological Correlation between Previous and Current Diagnosis of the Tumor subtype Variants:

Tumor type	**Tumor subtype**	Histopathological correlation (Agree)	% correlation
Neuroepithelial tissue Tumors (‘’Gliomas”)	Diffuse Astrocytoma	2/2	100.0
	Anaplastic Astrocytoma	1/2	50.0
	GBM	6/7	85.7
	Oligoastrocytoma	0/1	0.0
	Pilocytic astrocytoma	18/18	100.0
	Pleomorphic Xanthoastrocytoma	1/1	100.0
	SEGA	2/2	100.0
	Ependymoma	0/2	0.0
	Anaplastic Ependymoma	4/4	100.0
	CP Papilloma	1/1	100.0
	Ganglioglioma	2/2	100.0
Sellar Region Tumors	Craniopharyngiomas	10/11	90.0
Medulloblastoma (Embryonal Tumors)	Classic Medulloblastoma	15/15	100.0
	Desmoplastic Medulloblastoma	4/4	100.0
	Medulloblastoma with extensive nodularity	1/1	100.0
Meningioma	Atypical Meningioma	3/3	100.0
	Meningoethelial Meningioma	1/1	100.0
	Syncytial Meningioma	3/3	100.0
	Transitional Meningioma	1/1	100.0
Pineal Region Tumors	Pineoblastoma	1/1	100.0
PNET	PNET	3/5	60.0
TOTAL (N)		87	

The table above showed the level of correlation between the various tumor subtypes on regards to their previous (The original histopathological diagnosis) and current histopathological diagnosis. (after tumor review morphologically by the two supervisors and necessary IHC done). The overall level of correlation for all the tumors is 90.8%. The table summarizes all the tumors in the study and their level of correlation.

HISTOPATHOLOGICAL CORRELATION (PREVIOUS AND CURRENT DIAGNOSIS) OF THE VARIOUS TUMOR TYPES.

N=87 cases

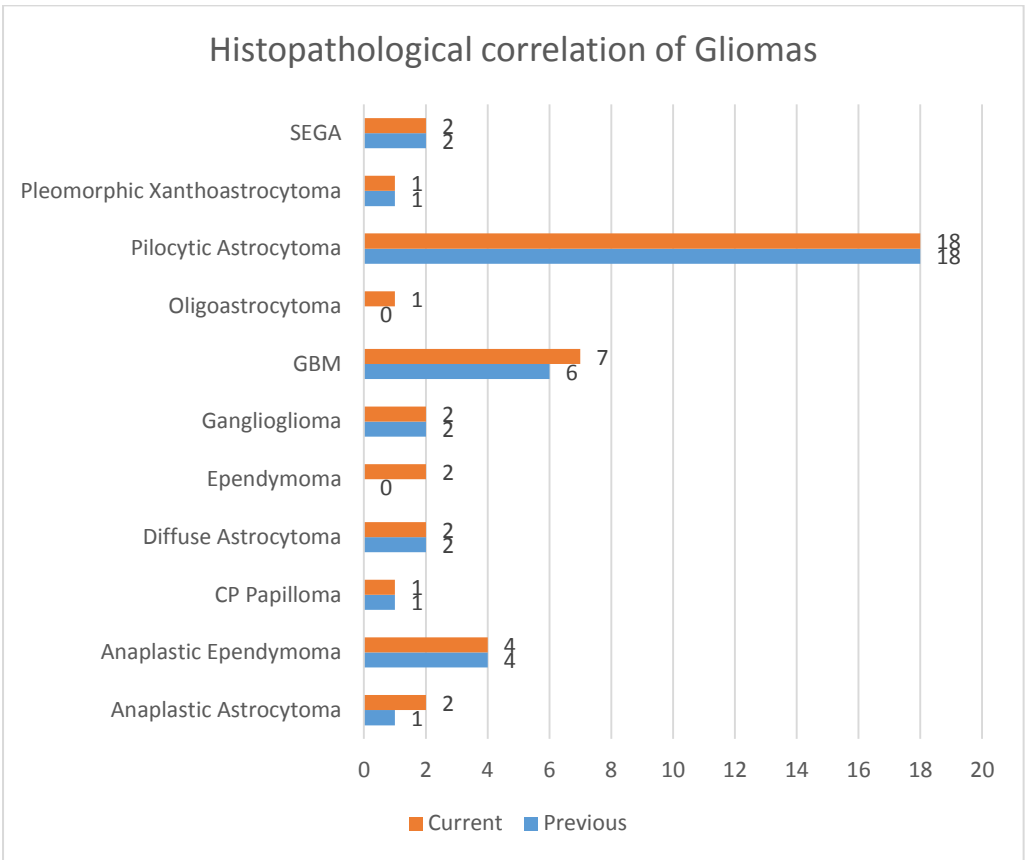


Figure 13: Histogram showing histopathological correlation of Neuroepithelial tumors ('Gliomas')

Most of the tumors had 100% correlation with the exception of ependymomas which had the highest discordance at 2 cases followed by oligoastrocytoma, GBM and anaplastic astrocytoma each with a single case. (Figure 13)

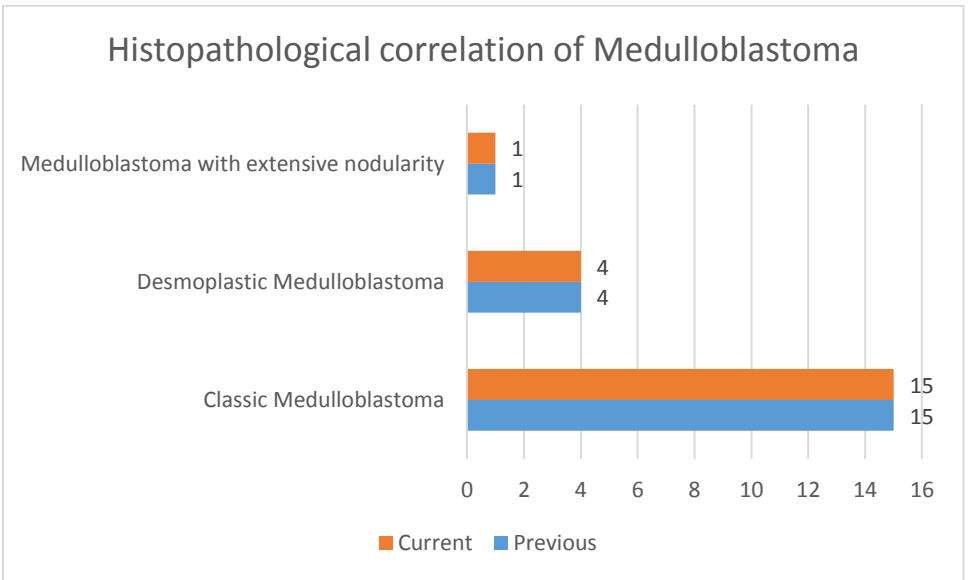


Figure 14: Histogram showing histopathological correlation of Medulloblastoma

All the medulloblastoma variants/subtypes had similar correlation (100%) morphologically as indicated above (Figure 14).

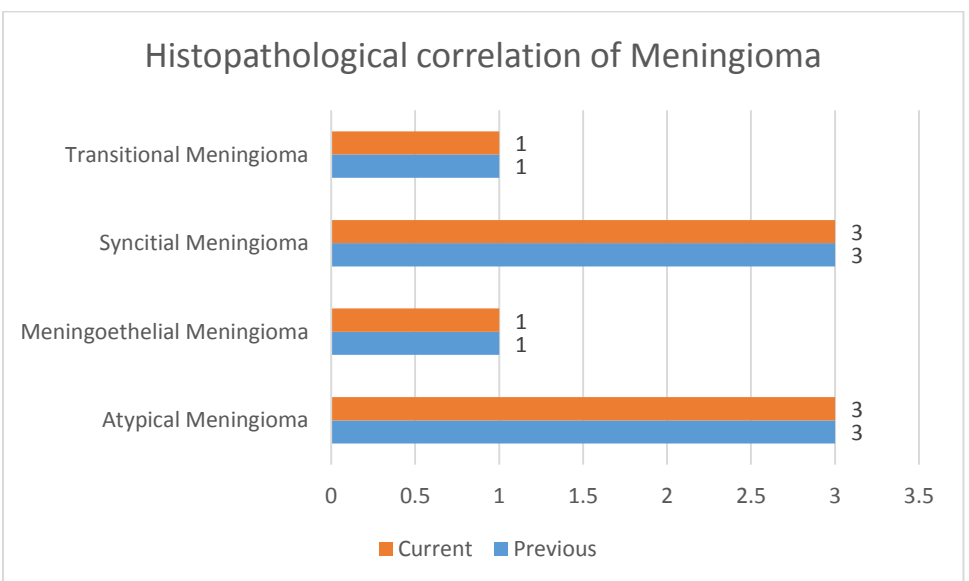


Figure 15: Histogram showing histopathological correlation of meningioma

There was 100% correlation morphologically between the previous diagnosis and subsequent histopathological diagnosis after review by the two pathologists. (Supervisors) (Figure 15).

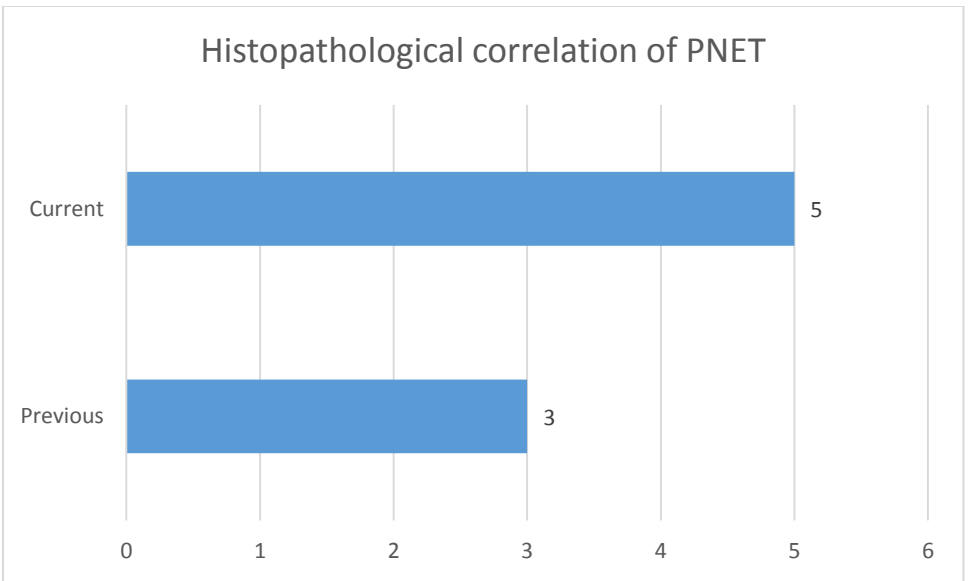


Figure 16: Histograms showing histopathological correlation of Pnet

The figure above showed the level of correlation between the various Pnet types with regards to their previous (The original histopathological diagnosis) and current histopathological diagnosis. (After tumor review morphologically by the two supervisors and necessary IHC done). Pnet recorded a 60% correlation (Figure 16).

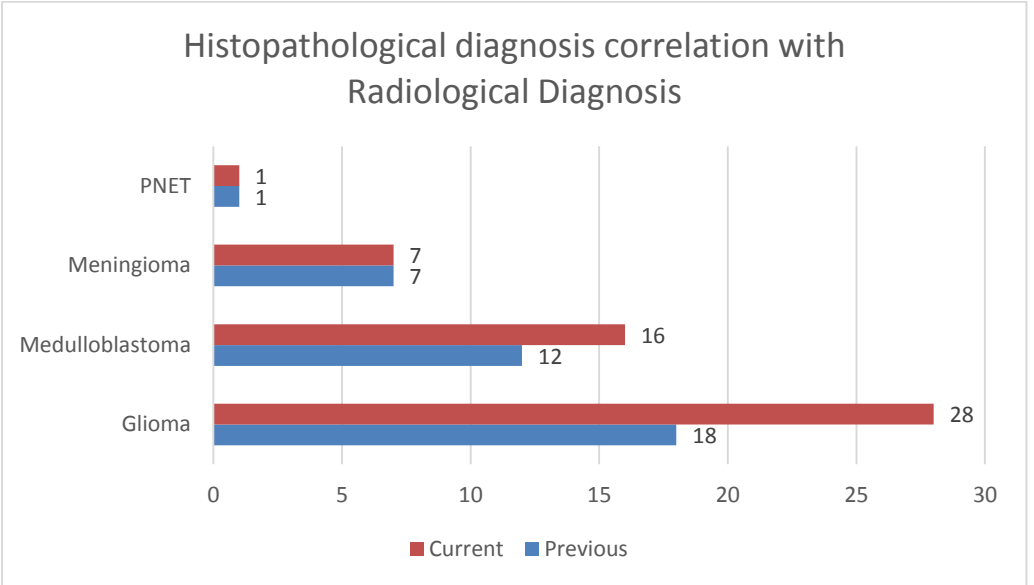


Figure 17: Histogram showing Correlation between Imaging (MRI or CT-Scan) findings with final histopathologic diagnosis

The overall correlation for diagnosis of the various tumor types by radiology is as indicated above. Respective correlations in diagnosis of the tumor types i.e. meningiomas, Pnet were highest at 100% followed by medulloblastomas at 75% with gliomas at 64.3% (Figure 17).

		Histopathology		Total	Kappa	p-value
		True	False			
Imaging	True	34 (69.4)	3 (75.0)	37 (69.8)	-0.024	0.814
	False	15 (30.6)	1 (25.0)	16 (30.2)		
Total		49 (100.0)	4 (100.0)	53 (100.0)		

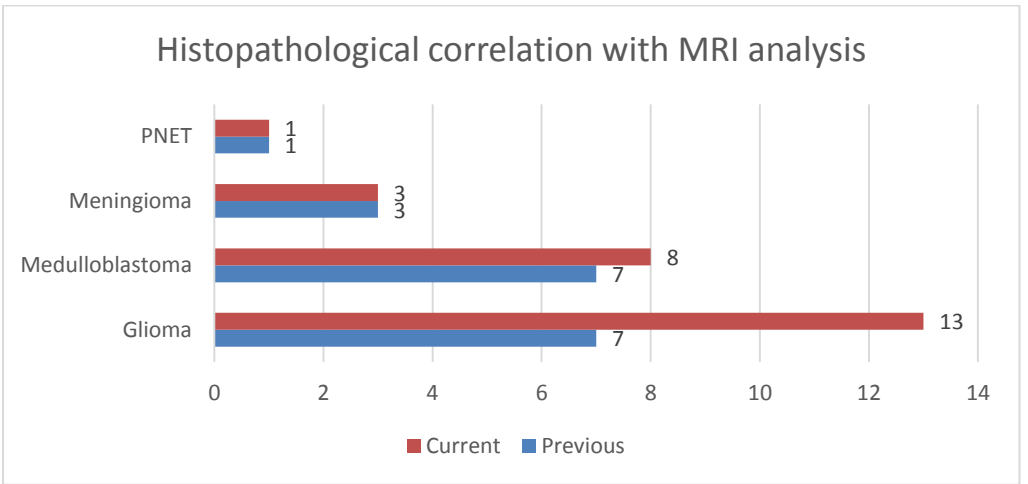
		95% CI
Sensitivity	69.39%	54.58% to 81.75%
Specificity	25.00%	0.63% to 80.59%
PPV	91.89%	86.20% to 95.36%
NPV	6.25%	1.15% to 27.71%

Table 6: Correlation between Imaging and Histopathological diagnosis

The table above showed the correlation levels between imaging and histopathology which are noted to be insignificant with respective P and Kappa values. The sensitivity and specificity in diagnosis of brain tumors by radiology was at 69.4% and 25% respectively.

Correlation of the various Tumor type diagnosis with respective Imaging modalities

N=25 cases



N=28 cases

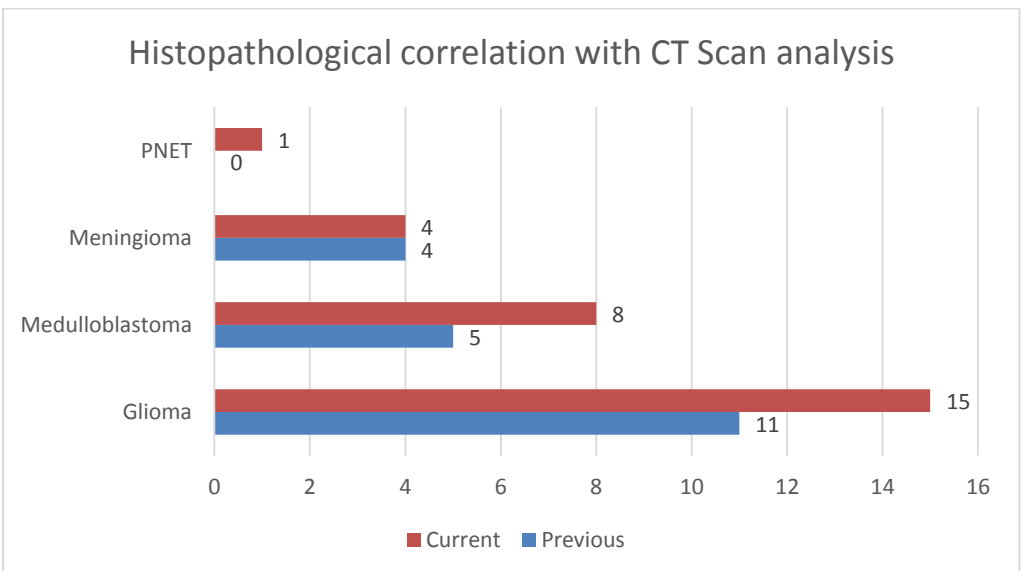


Figure 18: Histograms showing correlation of the various Tumor type diagnosis with respective Imaging modalities

MRI demonstrated 100% correlation in diagnosis of meningiomas and Pnet followed by medulloblastoma at 87.5% and the least being gliomas at 53.8%. CT scan on the other hand demonstrated 100% correlation in diagnosis of meningiomas followed by gliomas, medulloblastomas and Pnet at 73.3%, 62.5% and 0.0% respectively (Figure 18).

CHAPTER 5

DISCUSSION

Brain tumors are the most common types of solid tumors in children under the age of 15 years in developed and developing countries with 30,000-40,000 children being diagnosed (35,36). They are similarly known to be the most common cause of cancer deaths in children worldwide (1). It has been noted that childhood brain tumor data have not been well segregated from adult tumors especially in developing countries (30,37). Few studies though have been conducted with attempts at delineation with findings showing an increasing trend of paedriatic brain tumor cases. A case in point is a review of paediatric neoplasms from Ibadan, Nigeria which documented a six-fold increase (2.2% to 12.9%) in the relative frequency of paediatric brain tumors over a period of five decades (4).

In most of the literature available there is increasing incidence of most variants of brain tumors with increasing age which has been linked to the length of time exposure required for neoplastic transformation, the need for genetic changes to take effect prior to onset of clinical disease and more often due to reduced immune surveillance (38). This explains why majority of the brain tumors are more common in adults as compared to children. However over time, there has been increasing brain tumor incidences in children as well, a case in point being a study by Idowu et al 2007 which revealed that 37% of all CNS neoplasms occurred in children (30). This significant increase had been attributed to availability of more sensitive neuroimaging modalities (39,40). Further assessment of this trend especially in our settings would be useful besides characterization of the tumors.

There are logistical challenges experienced in conducting population based studies of brain tumors among which includes accuracy of the diagnosis, tumor classification and coding among different cadres hence most of the data are hospital based. This study aids to provide a hospital based data from two settings in the country in view of the fact that they both receive majority of the neurosurgical cases being the two leading referral institutions in the country. The study involved evaluation of the demographical profile, histopathological and neuro-radiological correlation of the brain tumor variants in the two settings with a view of critically assessing the various diagnostic parameters. In our study there were 87 histopathological cases of brain tumors in children in KNH and MTRH over a three year period, from 1st January 2015 to 31st December 2017.

The mean age of the children in our study was 7.9 years which is comparable to most studies in Africa and around the world. A study by Olabiyi et al 2016 in Nigeria had a mean age of 7.3 years and one in Korea with a mean of 7.8 years (3,41). One study showed relatively higher mean age i.e Uche et al 2013 in Nigeria which had a mean of 9.3 years while other studies from Germany, Pakistan and Iran which had mean ages of 10.7, 8.8 and 8.8 years respectively (22,26,42,43).

The study found out that more females than males were affected by brain tumors i.e. 47 females and 40 males (54% and 46% respectively) with a male to female ratio of 0.85:1 which was statistically insignificant. These findings were similar to studies by Olasode et al 2000 and Wahome et al 2001 both of which showed a higher female preponderance (37,44). On the other hand, other studies have showed a higher male to female preponderance including Olabiyi et al 2016 and Mehdi et al 2010 (41,42,

45,46,47,48,49,53). Similar findings have been noted from studies in Germany, Iran, Japan , China and India (22,42,50,51,52).

In our study 48.3% of the brain tumors were distributed in the infratentorial compartment and 47.1% being in the supratentorial compartments. This finding is contrary to studies by Wahome et al 2001 within KNH and those from China, South Korea, India and Brazil showing a preponderance for supratentorial tumors (41,44,51,52,54). Other contrary findings are noted in other settings, for instance in Nigeria, Olabiyi et al 2016 revealed an almost equal ratio between supra- and infra-tentorial tumors as well as findings of Kaatsch et al 2001 and Mehrazin et al 2007 in Germany and Iran respectively (22,42,45).

Worldwide, central nervous system tumors account for 20% of all childhood brain tumors with majority of up to 70% arising from the posterior cranial fossa (Infratentorial) (59). This is reflective in our study where 48.3% of the tumors arose from the infratentorial compartment. In our study it was noted that gliomas most commonly occurred in the infratentorial area at 20 (23%) followed by supratentorial area 19 (21.8%), thalamus and brainstem regions in the descending order. This is in contrast to adult brain tumor studies where frontal lobe is regarded as the commonest location for gliomas due to its higher brain matter volume. Another case in point which contradicts the findings in paedriatic and adult glioma location is a study by Suvi L et al 2007 which found out that 87% of adult gliomas were in the cerebral lobes and the frontal lobe was the most common site at 40% followed by the temporal lobe and the parietal lobe in that order. (60) All the medulloblastomas were located in the infratentorial compartment with

Pnets, meningiomas and craniopharyngiomas being mainly located supratentorially. Most of these findings are similar to most of the literature findings available.

In our study, the main tumor types were gliomas (48.3%) followed by medulloblastomas (23%), craniopharyngiomas (12.6%), meningiomas(9.2%), Pnet (5.75%) and pineoblastoma being the least. Gliomas in this case includes astrocytoma, ependymoma, glioblastoma, oligodendroglioma and various subtypes and combinations. Generally, the main tumor groups in children worldwide are astrocytomas (38-50%), ependymoma (8-14%), primitive neuroectodermal tumours (PNET), medulloblastoma(16-25%), and other gliomas (4-16%).(25) Rickert et al 1997 in their meta-analysis with other studies noted that astrocytoma ,medulloblastoma, ependymoma, and craniopharyngioma in descending order of incidence were the most common types of brain tumors in paedriatic and adolescence population. (41,42,48,61) These findings are similar to most studies in Africa just as in developed countries where the most common pediatric brain tumors are astrocytomas (gliomas) and medulloblastomas (10,57,62,63,65,66,67). Olabiyi et al 2016 in Nigeria recorded astrocytic tumors as the most common at 25.9%). (45). Within our settings and KNH in particular most of the studies have either been adult- based or involved the general population most of which are in agreement with our findings. Kibaya G et al 1999 found out that gliomas accounted for 36% followed by meningiomas at 14%.(17) Chumba D et al 2006 noted that gliomas accounted for 48%, a figure that was basically the same for meningiomas.(68) Mwang'ombe et al 2005, Zuriel et al 2008 and Wahome et al 2001 had similar findings with gliomas being predominant.(18,27,44) Boore et al 2008 on the other hand found out that meningiomas were more common than gliomas. This was not conclusive since meningiomas were the most frequent tumours operated on in KNH at the time with the study using

intraoperative cytological smear as study specimens as opposed to tumor biopsies in all the other studies. (69)

In our study, several brain tumor types were more common in females than in males (tumor ratio was >1) including gliomas, craniopharyngiomas and Pnet while medulloblastoma and meningioma recorded similar occurrence among the genders. A case of pineoblastoma was however noted in the male gender. This finding is similar to Mehdi K et al 2010 which had several brain tumor types which were more common in females than in males (tumor ratio was >1) including diffuse astrocytomas, ependymomas, craniopharyngiomas, anaplastic ependymomas (grade 3) and choroid plexus tumors and in contrast to meningioma type which had equal representation among the genders in our case. (46) In related studies Cho et al 2002 reported a higher male preponderance in oligodendroglial tumors similar to our case. (41)

In our study, astrocytic tumors were the commonest primary CNS and gliomas in children in our study at 37.9% of all the primary childhood brain tumors and 78.6% of all gliomas. This is relatively similar to most studies in Europe, Asia and South America which have a range from 30.5% to 47.3 % of all the paedriatic brain tumors. (70,71). Other settings reported medulloblastoma as the most common brain tumor (34.5%) followed by pilocytic astrocytoma at 17.3 % (66). Similar findings were noted in other studies including the Pakistan study reporting a 45.6% medulloblastoma occurrence. (1,24,41,42,48,72) Olabiyi et al 2016 noted medulloblastoma as 3rd most common tumor in the series (16.8%) after ependymoma which is quite rare in our settings.(45) In our study, medulloblastomas accounted for 23% of all the primary childhood brain tumors and ranked as the second commonest tumor type. It's classic subtype variant was

ranked as the most common at 75% which is consistent to most studies in literature. On the other hand, the desmoplastic/ nodular variant which is mainly found in infants was recorded at equal proportions in the 5-9 and 10-15 yr. age range. The most common astrocytic tumor in our study was pilocytic astrocytoma at 42.9% of all the gliomas and 20.7% of all the primary childhood brain tumors being 2nd to medulloblastomas. This is in agreement with a study by Wahome et al 2001 at 24.3% occurrence with a majority of the study subjects being within the first two decades of life. (44). This tumor had equal representation among the two genders in our study. It was commonest among the 10-15 year age group followed closely by the 5-9 year age group. This is reflective of most findings in literature with its non-predilection in gender and arising mainly within the first two decades of life. However in Zuriel et al 2008, the bulk of pilocytic astrocytomas were recorded among females at 64.7%. (18) This can be due to the fact that both childhood and adult brain tumors were sampled. In our study grade II astrocytomas occurred in 8 cases (19%) of all the gliomas which is much lower as compared to Wahome et al 2001 study where 75% of all grade II astrocytomas occurred at ages below 15 years.

Worldwide, the overall incidence of ependymomas in large studies has been reported as being 4.7% of all CNS tumors and 9.1% of all gliomas.(44) Olabiyi et al 2016 ranked it as the second most common tumor at 19.5% of the cases.(45) Ependymoma, which has been more commonly reported in other studies of pediatric brain tumors was recorded in six cases (6.9%) of all the brain tumor cases and 14.3% of all gliomas.(37,67,74) This is similar to other studies which have ranges from 4.8% to 10.5% of all the paedriaric brain tumors. (22,42,43,52) In Olasode et al 2000 study of over a decade, no case of ependymoma had been reported. (37) In our study, it was among the least common

tumor types and were reported more in females (4 cases) which is in contrast to other studies (43).

Craniopharyngiomas was noted in 11 cases representing 12.6% of all the childhood brain tumor cases. It was the third commonest tumor type after gliomas and medulloblastomas. Majority of these tumors were adamantinomatous and equally distributed in the 5-9 and 10-15 yr. age range similar to most studies where adamantinomatous variants are more common than papillary variants and peak age is usually at 5-10years. In our study it was more common as compared to ependymomas. This is in contrast to Mehdi et al 2010 where ependymomas were more common than craniopharyngiomas. (46)

In our study, there were 8 (9.2%) cases of meningioma among the brain tumor variants. This is in sharp contrast to most of the adult tumor studies which ranks it as among the most common tumors.(27,28) Uche et al 2013 ranks it as the least common with a single case reported.(26) . In most of the literature its occurrence has a female predilection contrary to our study where both gender is equally represented.

Majority of the tumors in our study were noted to be low grade (55.2%) with gliomas leading at 69% which is a significant factor as far as good prognostication is concerned. This tumor grade is often linked to a more benign, non-aggressive tumor and has a higher chance of good outcomes when management is instituted early. The presence of high grade tumors especially in gliomas emphasizes the need for better strategies in identifying these tumors early. The challenges are linked to the fact that majority of the tumors may have not being detected early owing to the referral systems in place and detection rates. Other tumor variants are aggressive from the onset hence are of a higher

grade morphologically. Majority of the glioma and all the meningiomas and craniopharyngiomas were benign while all the medulloblatoma, pineoblastoma and Pnet are malignant, the latter group of which similar to most literature available are based on their morphological characteristics.

In practice brain tumors morphologically tend to appear heterogeneous with a considerable within tumor and among tumor histopathological variation (75). Histomorphological features such as necrosis, vascular proliferation, and increased mitotic activity as much as are considered as features of high grade tumors, may not always be straightforward a case in point when delineating certain tumors for instance anaplastic astrocytoma, glioblastoma or mixed oligoastrocytoma. It is for this reason that in practice the initial histopathological diagnosis may not necessarily be the definitive final diagnosis. Other ancillary tests would be useful in better characterizing these tumors.

The leading causes of misdiagnosis in brain tumors include errors during biopsy, histopathological variations in regards to type of biopsy retrieval techniques i.e. stereotactic (microsurgical resections) and resection diagnoses, incorrect interpretation of microscopic features of tumoral tissue and the interobserver variation between tumor variants and grades during morphological assessment (76,77). The latter has been extensively reviewed by Scott et al 1995, Van D et al 2010 and Hildebrand et al 2008 who noted a high degree of discordance in brain tumor histopathological diagnoses especially in astrocytomas (77,78,94). In another study by Jackson et al 2001 who assessed the discrepancy in diagnosis of glial tumors, the study noted an existence in 49% of the tumors which were later reviewed to 38% , as likely to have affected the

prognosis and treatment modalities in 26% (79). In our case the level of agreement was at 88.1% of all the gliomas which is three times lower in discrepancy as compared to the latter's study. In most studies especially in glioma studies, the level of agreement was noted to be more than 50% which is similar to our study (80,81,82,83). With regards to the type of tissue retrieval techniques, a study by Chandrasoma et al 1989 involving histopathological variation in stereotactic and resection diagnoses, correlation was noted between 19 out of 30 tumoral cases (63.3%) (84). This serves as a true reflection that the amount of tumor biopsied contributes to the final diagnosis made. In both our set ups on the other hand, majority of the histopathological diagnosis made are usually from resection biopsies which provide a more extensive and efficient diagnosis. Interobserver variability has been a leading contributor to variations in morphological diagnosis of brain tumors worldwide. This has been linked to subjective diagnostic criteria, overlapping morphologic features, and variations in training and practice among the pathologists (85). This can be improved through team work review of the cases and currently through immunohistochemical and molecular analysis. In a study by Duffner P et al 1986, concordance was at 50% among experienced neuropathologists in classifying and grading oligodendroglioma, astrocytoma, and oligoastrocytoma (64). This correlation was noted to have improved to 70% after the pathologists reviewed the tumor cases together and discussed the necessary diagnostic criteria. Coons S.W, et al 1997 study described a concordance of 50% among four neuropathologists examining diffuse astrocytomas. This review has been extensively studied in various institutions with improved outcomes with some centres coming up with a central review systems.(82) This has been replicated in our study where two pathologists reviewed the cases together and incase of variations adjunct tests were conducted. The level of

correlation histopathologically with respect to previous diagnosis provided in our study was reported at 90.8% overally which is significantly higher as compared to the above studies. This confirms that through morphology alone and with team work review of the tumors and hopefully adoption of a central review team, majority of brain tumors can be positively diagnosed. This is crucial especially in far flung centres/ health facilities where access to adjunct tests may be lacking. Majority of the inaccuracy in histopathological diagnosis were noted in ependymomas and Pnet at two cases each. The rest i.e. anaplastic astrocytoma, craniopharyngioma, GBM and oligoastrocytoma had a single case each. In all these cases, immunohistochemistry was conducted with all the findings similar to the diagnoses made after second review of the tumor blocks emphasizing the need for teamwork review or a centralized review team.

The immense contributions adjunct testing adds in improving final histopathological diagnosis cannot be overlooked. This is in regards to immunohistochemistry and molecular characterization which has a critical role in prognostication besides characterization of the tumor. The current WHO brain tumor classification 2016 has incorporated these diagnostic modalities with molecular characterization being superior. This is indicated in studies by Nutt et al 2003 among other studies which found out that classification of glioblastomas and nonclassic anaplastic oligodendrogliomas based on gene expression showed a significantly better correlation with survival than histological classification. (86,87,88) The challenges noted in many developing countries as well as both in our settings are the unavailability and expensive costs of some of the tests. The WHO 2016 classification utilizes panels e.g. IDH in distinction of the various glial tumors. These panels were unavailable in the major and other health facilities and are quite expensive if available. Molecular techniques i.e PCR can be used to further

characterize these tumors as world type, mutant which are useful markers as far as response to chemotherapy and prognostication is concerned. Our study for instance utilized the previous standard panels for distinction of the various tumors e.g the use of GFAP which is positive for glial tumors to distinguish from PNET which are CD99 positive but GFAP negative. However, a few inexpensive immunohistochemistry tests much of which were applied in the study are significant in making prompt distinctions among major tumor variants. The adoption rates by the settings for these tests were quite low contributing to the significant discrepancies hence the need for adoption of these methods to enhance tumor diagnosis.

Generally in practice, it is not easy for clinician to diagnose brain tumor with specification after clinical evaluation hence the need for imaging modalities for characterization. Moreover, it is also not easy for a radiologist to diagnose some brain tumors with certainty due to the fact that different brain tumors may show similar radiological features which makes the differentiation of these tumors by imaging alone difficult.(17) Imaging as a diagnostic modality has its challenges which would then tend to affect the final diagnosis. This can be attributed to various reasons. Kibaya G et al 1999 noted that in 20 (13.3%) of the cases the radiological diagnosis was reported as nonspecific a fact which was attributed to lack of proper clinical information.(17) Lwama et al 1991 study though proving that MRI was by far superior in analyzing brain tumors to CT scan, noted no signal intensities correlation with tumor malignancy and no correlation between signal intensities of gliomas and tumor grades in MRI proving that imaging as a technique may have challenges in categorization of the various tumor grades (89). This is replicated in a more recent local study by Abuodha M et al 2013

who focused more on meningiomas and documented limitations of MRI in categorization of the tumor subtypes (15).

Studies have been conducted to assess correlation between imaging and eventual histopathological diagnosis of brain tumors which has led to the development of location-wise radiologic diagnostic algorithms purposed to assist pathologists in narrowing down histopathologic diagnosis during morphological assessment. A case in point is a study by Ishita P et al 2015 in which 100% correlation was noted in infratentorial extra-axial tumors with a majority of the locations showing correlations of over 90%.(90) This indicates that imaging as a tool can enhance diagnosis and be used as a guide by pathologists in diagnosis of brain tumors. The overall sensitivity in diagnosing brain tumors by radiology in our study was reported at 69.4% with correlation levels at 100%, 100%, 75% and 64.3% in Pnet, meningioma, medulloblastoma and glioma respectively. This is much lower as compared to studies by Kazem et al 2015 and Pant et al 2015 which reported the sensitivity level of histopathological diagnosis of tumors through imaging at 95.5% and 97% respectively. (91,92) The level of correlation in our study is however much higher as compared to Kibaya G et al 1999 and Zuriel et al 2008 study where sensitivities were reported at 40% and 16% respectively in KNH. The correlation levels within our setting could even be higher owing to the limitation that the study relied on diagnosis of the imaging whether conducted within and outside the two settings not putting into consideration the neurosurgical's team diagnosis input upon review.

To enhance level of correlation in diagnosis of brain tumors, some studies have recommended that pathologists prepare slides from the entire surfaces of the tumoral

tissue for microscopic evaluation. The use of whole paraffin block assessment approach has been noted to increase accuracy in diagnosis by improving histopathological feature appraisal of tumors. Neurosurgeons have also been advised to follow protocals in maximal tumor safe resection which enhances enough tumor sample availability and consequently facilitates correct pathological confirmation. Moreover, in other settings it has been recommended that clinicians be advised to make clinical judgements based on microscopic description of tumoral tissue and clinical-radiological presentation of cases. In case of discordance, central or team review/ consultations and relevant immunohistochemistry protocols recommended. (93)

In summary our study lays emphasis to the fact that a brain cancer registry is needed to fully understand the epidemiologic distribution of brain tumors. The establishment of such a registry would allow for better understanding of the pediatric tumor burden which would allow for standard diagnostic, treatment and financial/budgeting protocols to be developed.

CONCLUSION:

1. Gliomas and medulloblastomas are the commonest tumors at both centers similar to findings at centers in other studies around the world.
2. Histopathological diagnoses have a high concordance of agreement among various morphologists.
3. Level of correlation between histopathological and radiological diagnosis was high comparable to other findings conducted elsewhere within the country.

Recommendations:

1. A standard neuro-radio-pathological proforma is recommended which synchronizes significant clinical, radiological and pathological details within the two departments with a view of ensuring data availability and synchronicity.
2. There's need to expand the study to other centers in the country to gain the spectrum seen in the country.
3. There is a need for follow up of the patients because of the discrepancies in their diagnoses.

Limitations of this study:

1. The current classification of the tumors had to be categorized based on the previous WHO criteria i.e. 2007 for correlation purposes limiting further characterization of the tumors.
2. Some of the current/latest IHC panels which would have been employed were unavailable even in major facilities e.g. IDH, ATRX hence the reversal to standard/original panels e.g. GFAP, CD99, EMA and cytokeratin which effectively aided in the distinction of these tumors as indicated in table 4.

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APPENDICES

APPENDIX I: Procedure for Immunohistochemistry

1. Identify the wax blocks and make slides.
2. Dewax sections and transfer to 100% alcohol.
3. Block endogenous peroxidase with 0.5% hydrogen peroxide in methanol- 30 minutes.
4. Place in tris- saline buffer at 20C.
5. Antigen retrieval is done by heating the tissue sections in a microwave oven before immunostaining.
6. Wash in several changes of tris- saline at 20C.
7. Treat with P.B.S containing 1% normal serum (P.B.S/N.S) from the species the secondary to be rinsed for 2-5min.
8. Treat with specific primary antibody diluted to the order 1:100 to 1:250 for immunoglobulins or 1:250 to 1:500 for hormones with P.B.S/N.S – 30 min in a damp chamber.
9. Wash in P.B.S/N.S for 2-5min
10. Treat with secondary antibody diluted in 1:40 with P.B.S- 20min
11. Wash with P.B.S/N.S for 2-5min.
12. Treat with P.A.P diluted 1:40 with P.B.S- 20 min.
13. Wash with P.B.S/N.S for 2-5min.
14. Rinse in 0.05M pH5 acetate buffer for ethylcarbazole
15. Treat with peroxidase substrate solution…ethylcarbazole or DAB for 5 min.
16. Rinse in distilled water.
17. Stain in Mayer’s haematoxylin- 30seconds.
18. Wash and blue in running water
19. Mount in glycerin jelly or a suitable aqueous mountant.

APPENDIX II: Specimen Preparation

1. Once received the gross specimens placed in formalin are recorded using the patients inpatient number and at the same time given a special histopathology laboratory number. Incase not fixed then the gross specimen can be placed in an appropriate fixating agent.
2. Grossing of the specimen can then be carried out using the standard grossing techniques into smaller sections which are then placed in a cassette for subsequent processing.
3. Tissue processing either manually or by the use of a tissue processor is hence carried out up to the extent in which the wax embedded cassettes are retrieved. Most of the block cassettes for the purpose of the study will be retrieved at this level.
4. Sectioning of the tissues is then carried out using a microtome which cuts up the section to single layer of cells usually between 3-5 micrometer.
5. Sections are then "floated out" on the surface of warm water in a flotation bath to flatten them and then picked up onto microscope slides. After thorough drying they are ready for staining.

APPENDIX III: Haematoxylin and eosin staining preparation

Reagents

4. Eosin 1% aqueous solution

   Eosin 10g distilled water- 1litres

5. Harris-haematoxylin solution

   Haematoxylin-5g

   Ethyl alcohol-50ml

   Ammonium aluminum -100g

   Distilled water-1 liter

   Mercuric oxide red 2.5g

6. Scotts tap water

   Na hydrogen carbonate-3.5g

   MgSo4 -20g

   Distilled water-1 liter

   Acid alcohol

   -0.5%hcl in 70% alcohol

Procedure for staining

1. Dissolve the ammonium aluminum in distilled water heat, stirring frequently.

2. Dissolve the haematoxylin in the alcohol and add to aluminum solution.
3. Bring to the boil while stirring.

4. Mix and allow cooling.
5. Filter into a glass stain bottle and the solution is ready for use.
6. De-wax sections with two changes of xylene.
7. Re-hydrate sections with two changes of absolute alcohol and wash in running tap water.
8. Stain with haematoxylin sol for up to 5 minutes.
9. Wash in running tap water.
10. Differentiate in acid alcohol for approximately 5 minutes.
11. Wash in running tap water.
12. Blue in Scotts tap water for few seconds.
13. Wash in running tap water.
14. Stain with eosin for approximately for 5 minutes.
15. Wash in running tap water.
16. Dehydrate, clear and mount section.

APPENDIX IV: **CBT Proforma Tool:**

Information on request form (part a)
Lab Number: .....
Study Number: .....
Name……..... Age: _____*years.*
Sex: 1. Female 2. Male Date:……..
I/P NO:

Radio (N/Surg) diagnosis_____
Prev. H/Path Dx_____
Intraoperative information Site: (tick)

1. Frontal_____(__)
2. Parietal_____ (_ _)
3. Temporal_____(__)
4. Posterior cranial fossa_(__)
5. Midbrain_____(_)
6. ventricular_____(_)

HISTOLOGICAL INFORMATION: **(part b)**
Tumor Type: _____
Tumor Subtype: _____
Tumor Grade (WHO): _____
Tumor Grade (High or Low):_____
_____

HISTOLOGICAL REPORT
IMMUNOHISTOCHEMISTRY:
IHC Recommended?
Antibody Type/Types recommended: _____ _____ _____
Result: _____ _____ _____
Final diagnosis: _____
Grade:

Signature:
Pathologist ( )

Modified Proforma (34) “Dataset for tumors of the CNS- Royal College of Pathologists- 2016”

APPENDIX V: Dummy Tables of Analysis
Descriptive Analysis Table

SOCIO-DEMOGRAPHIC DATA

INDEPENDENT VARIABLE-AGE(years)	NUMBER	PERCENTAGE
Less than 5 years		
5-9		
10-14		
15-20		
GENDER		
Male		
Female		

TUMOR TYPE AND SUBTYPE:

TUMOR TYPE	TUMOR SUBTYPE	PERCENTAGE

VARIABLE-TUMOR LOCATION/TYPE	NUMBER	PERCENTAGE
INFRATENTORIAL		
SUPRATENTORIAL:		
BRAINSTEM		
CENTRAL		
THIRD VENTRICLE		
TECTUM		
PINEAL GLAND		
PITUITARY GLAND		

THALAMUS		
HYPOTHALAMUS		
OPTIC PATHWAY		
BASAL GANGLIA		
OTHERS		

TUMOR GRADE (WHO)	NUMBER	PERCENTAGE
I		
II		
III		
IV		

TUMOR GRADE.	NUMBER	PERCENTAGE
LOW GRADE		
HIGH GRADE		